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WHAT IS PSYCHOLOGICAL MEDICINE?

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PART I

INTRODUCTORY

"ALL GOOD OR EVIL, whether in the body or in human nature, originates in the soul and overflows from thence. Therefore, if the body is to be well, you must begin by curing the soul. The cure has to be effected by charms of fair words; temperance is emplanted in the soul and health is then steadily imparted into the whole body. It is the great error of our day in the treatment of the human body that the physicians separate the soul from the body." (Socrates)

I grieve to say that these pronouncements of the Master Mason, who erected the edifice of philosophy, are as true today as they were over two millenia ago. Consequently, the rest of my essay will be a mere elaboration.

I think it was another philosopher belonging to our own craft, Sir Clifford Allbutt, who said that of all things in medicine, definitions are the hardest. Yet in no other branch of it is clear meaning of word-symbols (semasiology) more crucial than in this one now under our scrutiny.

The psyche, or mind, may be defined negatively as that part of the total person (personality) which is intangible; that is, it cannot be directly appreciated by our crude five senses. It is an abstraction which can only be inferred (or appreciated indirectly) in others, from their behaviour (including speech); and in ourselves, it can be felt directly through introspection. Or, more positively (psycho-physiologically) it is that part of us which receives (perception) stimuli from the outer and inner worlds which impinge on our sensorium. It assimilates them, associates them, organizes them, registers them (memory) and then reacts to them with emotions and rarely with thoughts which are finally expressed in action (motor behaviour) or speech.

It follows that, though the mind cannot be grasped, it is indeed more real than things physical. Hence, one can be more certain of its existence than of any other thing. Descartes' final analysis was "cogito ergo sum," and Berkeley's proposition was "nothing exists save an idea in the mind."

Psychology is the scientific (objectified) approach to normal mental processes and the personality as a whole. It seeks to measure.

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Psychiatry is that branch of Medicine concerned with the study of mental disorders and their treatment.

Psychosomatic medicine is the simultaneous study and treatment of psychic and somatic factors leading to dysfunction. It is concerned with uncovering relationships between these mental and physical aspects of a person and his environment. Ideally, all medicine is psychosomatic.

Psychopathology is the dynamic formulation of various processes leading to a morbid mental state. It overlaps the study of the normal mind (psychology) and, thus, does not provide an equivalent link in the chain of:

Anatomy → Physiology → Pathology → Medicine → Therapy.

But this chain can be restored by adoption of yet another term; thus:

Psychodynamics → Psychopathology → Psychiatry → Psychotherapy.

Its main function is to provide a logical basis for treatment.

Personality is the total being, the body-mind unity, that we all are, reacting in a total environment.

Environment, or milieu, is anything or everything in the outer world of a person.

BACKGROUND

Churchill once said, "The more one looks back, the further one can look forward." If we do this, we find that Psychiatry was born long before the rest of the corpus of Medicine. In the jungle of a quarter million years ago, it was the first cry of pain, of Heidelberg man, that had to be soothed—and the soothing was necessarily psychological, as was both the pain and its expression: crying. The physical means of treatment were not at hand. Throughout the animistic and most of the religious phases of civilization, the way to cure an illness was demonological—by magic or hoodoo practiced by the witch doctor. Trephining in the early Egyptian civilization (so reminiscent of modern "psycho"-surgery), was done to let the evil spirit out. In the days of Hippocrates, and even of Paracelsus, Medicine was better integrated, with no such artificial schism as there is today. In the Middle Ages, however, Medicine and Psychiatry parted ways, for, while the surgeons became skilled barbers and the physicians astute astrologers, the psychiatrists remained witches, and, occasionally, miracle-makers, and rarely philosophers. When Medicine emerged from the Dark Ages, say with Linacre and John Caius, in the 15th and 16th centuries, Somatic Medicine became luminous with Virchow in the 19th century and later Pasteur and Fleming in our own day. Psychiatry in the Western world remained darkened, so that the insane, shackled and manacled in irons, provided an amusing spectacle for the idle (by no means immune) rich at the Bedlam or other asylums. So the last witch was burnt on a stake in England barely two centuries ago. In the Eastern world, before Christ, the care of the mentally ill was humane, and the Siberian Shamas were skilled hypnotists.

The shackles were taken off by Pinel in France and Tuke in England, and shafts of light dispelled much of the cloud of fear. With Freud, a new era dawned so that, in the recent half-century, the mind has almost caught up with the body. Almost, but not quite. A glance back at the definition of mind will make it plain that everyone has

one—that it is quite the most important thing one has or comes across in others. Unfortunately, any human thing may go wrong, so that when it happens to the mind, it is a veritable calamity. Consequently, fear, or even terror, prejudice and dogma lead to a number of patterns of attitude. As we are touching on matters of the mind, it is meet that we should begin by an analysis of these attitudes towards it and towards those who study and treat its illnesses. The basis for these attitudes seems twofold:

1. A strong contrasting feeling: familiarity with the mind and fear of the unknown regarding it.
2. A human limitation, in that in order to function properly in the business of living, the mind must be as unaware of itself as it must be unaware of the normally functioning body. Hence, the enormous blind spot of those who are otherwise in possession of a sound mind. Prejudice, ridicule, rationalized dogma, scepticism, and even fear serve to cover up this blind spot.

Now these attitudes may be anecdotalized:

A. *The Lay Person*: There is the fear of losing the mind of the uneducated, and the uneasy ridicule of the educated (well exemplified by a present vogue of psychiatric humour). There is the foreign "mind-wizard" of Hollywood, the pukka sahib who knows his native, the Colonel who knows his men, the Pastor who knows his flock, and the political leader who knows his voters. Whereas they lack the armamentarium of a healer of the body, and hence give way to him, they feel they have it "instinctively" and do not give way to an expert of the mind.

B. *The Medical Person*: Though necessarily afflicted in the same way, he will be better defended by fortifying the somatic citadel. Hence, the need to find a physical substratum for "nerves." There is the skeptic who wants to prove "scientifically"; the practical man (like the Colonel) who dogmatizes "it is all common sense"—despite the assertion of the English humorist A. P. Herbert that such a thing is very uncommon; the keen young man who proves his diligence by inserting "psychogenic" at the bottom of a long list of differential diagnoses; the administrative man who leaves mental disorders out of his diagnostic returns; the wit who still thinks of Coué when he refers to a "trick-cyclist"; and the medico-legal man who admits "objective facts of behaviour as sole evidence." It is left to a few, with hindsight, and not all of them psychiatrists, to realize that Preventive and Psychological Medicine are the two branches of the highest social importance.

What is the practical importance of Psychiatry, and what are its boundaries?

It has been said that soon half the world will have to psychoanalyze the other half—and, if this were to keep both halves alive, it may not be too bad an idea. It has also been said that there are "white lies, red lies, and statistics," but statistics is one of the few methods of science (mathematics) applied to clinical medicine and it provides a use-

ful orientation. The following exceed the accuracy required by the usual run of clinical generalization and have been generally accepted. In the United States, 1 child in 27, and in the U.K. 1 in 30 born is likely to become mentally ill in the course of a few years. There are at least 5.8 mentally ill (institutionalized) in the U.S. and 3.2 in the U.K. per 1000 population. In addition, there is 1% suffering from mental deficiency. Both in Britain and in North America there are more hospital beds taken up by those mentally ill than by any others. In the ordinary mixed wards, 30% of hospitalized patients are neurotic (a higher proportion in some specialized wards such as for gastroenterology). This proportion of 1/3 is pretty universal for psychiatric casualties out of total casualties, both in war and in peace. Figures available from service induction centers in the last war show that 20% of the population (in the U.S., 2½ million men out of 15 million) is psychiatrically unfit for military service. It is commonly stated that 40% of general practice presents a psychosomatic (in the limited sense) problem. The pessimists say that in another generation or so, the entire population will be mad or idiotic—the scientists say this would merely establish another norm. A considerable amount of the national revenue is spent wittingly or unwittingly on emotional disorders. Yet, where the U.S. spends $400,000,000 on restaurant tips, the psychiatric services cost them only $180,000,000, unlike the $2,500,000,000 spent on other medical and dental services. Whereas $54,500,000 is given to medical research, only $2,000,000 is given to psychiatric research. From these considerations, and following the more "radical" literature, it would seem that medical education does not fit the doctor for his practice: only 4% of 5000 hours of training is given to this subject in American schools; elsewhere a proportion of these hours is optional. Of course, all clinicians claim (statistically) the importance of their subjects, and when Eyes and E.N.T. are added, the incidence of disorders rises to an unmathematical 500%. It is a matter of relative importance, but easy to see, that mental illness is most prevalent, lasting, and disturbing. As to the borderland of Psychological Medicine, I shall paraphrase Pasteur, and claim that there is none; alcoholism, selection of medical students, crime, ageing, the psychology of genius, education, divorce, V.D., industrial problems, racial and minority problems, war and social unrest, are all neighboring fields. But, to complete the paraphrasing, I believe that the individual psychiatrist should have well defined boundaries. The mind, apart from the above-mentioned morbid paths, has a habit of taking excursions into Religion, Art, Science, and Philosophy. Naturally, some of us must follow, but, equally naturally, these are by no means the happy hunting grounds of unaccompanied psychiatrists.

FOREGROUND

Having painted the background for you, it is now my purpose to sketch the foreground of my picture of Psychological Medicine by bringing to bear the usual headlines of clinical science.

Aetiology

There are other relationships between events than is depicted by a simple causal chain: there is parallelism, epi-

phenomenon and interrelationships as exemplified by cybernetics. The aetiology of mental disorders compared with physical disorders is like algebra is to $1 + 1 = 2$, e.g. iron deficiency in blood causes anaemia. This does not deny the necessity for such basic arithmetic. The governing principle which is seeping into the rest of medicine, is that of multiple aetiological factors and holism. That is, in the whole individual, there are a number of different factors, with relative weighting, which are brought to bear at different times and finally cause a breakdown in living (mental illness). These factors are viewed dynamically (unlike Virchow's cell). They are always moving in terms of development and decay, emotive reaction and its expression, stress and adjustive homeostasis. A pathogen is either a deviant from the social norm, or a stress in the psychosomatic structure, or an event rendered pathogenic by the special time of its application, e.g. puerperal depression. In an attempt at scientific orderliness, those factors could be divided academically into:

1) Hereditary and constitutional (including physical build, and personality structure in which congenital factors may also be operating).
2) Cultural and social milieu, i.e. ethnic, religious, economic, etc.
3) Psychological milieu, i.e. family and inner self.
4) Organic reactions, i.e. ageing.

Or, again, they may be more functionally grouped under:

a) Predisposing
b) Precipitating
c) Maintaining

} CAUSES

History and Mental Examinations

As you may realize, I prefer to use didactically these clinical methods by following the tradition of medicine and treating intangible matters of the mind as if they were (as indeed they can become) objective "systems." The history is paramount as it forms the scientific method of practice. Particularly that kind of science which Elliot calls functional as opposed to his absolute science, which Whitehead calls "essentially irrational" because "of the pursuit of crude and brutal facts . . . irrespective of its having any recognizable meaning." Yet, history taking, mental examination and the diagnostic formulation is also an Art. Not that there is a distinction between science and art at the conceptual level; they are both speculative in that every good piece of research comes through an idea—the inspiration is like that of a poet. The difference lies in the method applied to the idea. The method of history taking and mental examination follows historical and natural sciences in gathering grouped data, chronologically, and relating them systematically. The mental examination is an assessment, as individualistic as is the physical, based on concepts of anatomy, physiology, and embryology of the mind (to be discussed below). It is a time-consuming process; it needs verification from more than one informant (the patient) and elaboration. A thorough physical examination, when both the body and the mind's attitude to it are examined, is essential routine. Special investigation consists of: psychological testing, social work, electrophysiological methods (e.g. E.E.G.), biochemistry, and special neuropsychiatric methods.

A behaviour chart, though more complicated, could replace or accompany the temperature chart. I will not attempt to enter into detail regarding these methods. Suffice it to say that they are as various and as specific as their somatic equivalent; yet, they are necessarily more complex. When the data is complete, a diagnosis is arrived at.

A diagnosis, said George Bernard Shaw (the friend of Sir Almroth Wright) is finding out all that is wrong with a particular patient and why. So often it means the formal and unctuous pronunciation of a name. Equally "a case" is a condition of things which befalls a patient. A disease, as a morbid entity, is a myth created by the 19th century pathologist, unless it is a happening to a person who feels ill. What matters is the suffering, mental and physical, and its study beginning with symptoms or syndromes (symptom complex). And this is the beginning of a diagnosis. For convenience, diagnoses are then classified under an approved nomenclature. But they must be elaborated in a formulation which includes the main factors which cause the breakdown in living in that particular patient (at that particular time). Thus, Shaw's criteria must be satisfied.

Prognosis and Treatment

Prognosis and Treatment depend logically upon the diagnostic formulation. In treatment, as in clinical methods of investigation, there are many kinds of skill ranging from psychoanalytical methods to cruder physical attacks like prefrontal leucotomy. In the purely psychological method, the material used ranges from conscious (history) to unconscious stuff—e.g., dreams, free association, suggestion. The background for therapy is the all-important doctor-patient relationship, which, because of its strength, is called transference in this setting. It cannot be denied that therapy is also an Art, and that as such it completes in application where science leaves off in theory. It must be added, contrary to general belief, that psychotherapy is one of the most effective and most satisfactory methods of medical treatment. This is a real advance considering O. Wendell Holmes' witticism in the late 19th century, "with two exceptions, morphia and anaesthesia, the whole materia medica could be swept to the bottom of the sea and it would be better for mankind and worse for the fishes."

Note: The concluding article on "What is Psychological Medicine?" will appear in the February issue.

What I inveigh against is a cursed spirit of intolerance, conceived in distrust, and bred in ignorance, that makes the mental attitude perenially antagonistic, even bitterly antagonistic, to everything foreign, that subordinates everywhere the race to the nation, forgetting the higher claims of human brotherhood.

W. OSLER

THE GANGLIONIC BLOCKING AGENTS *

PHILLIP S. ROSEN, B.A., 5T2

INTRODUCTION

The autonomic ganglia consist of a large group of cell stations within the sympathetic and parasympathetic nervous system. The ganglia are innervated by many preganglionic fibres which reach them after leaving the spinal cord and travelling with peripheral nerves. Postganglionic fibres leave the ganglia and innervate smooth muscle, skin, heart and glands. In the sympathetic nervous system the preganglionic fibres are short, the ganglia lying at some distance from the effector cell, while in the parasympathetic system the preganglionic fibres are long, and the ganglia are often imbedded in the wall of the organ, or tissue, supplied. These ganglia, whether part of the sympathetic or parasympathetic nervous systems, have a similar pharmacological response to drugs, owing to the fact that the neurohumour necessary for nerve impulse transmission is the same for both, namely acetylcholine.

For normal impulse transmission through a ganglion two conditions must be fulfilled:

(a) Acetylcholine must be normally released.

(b) The released acetylcholine must be able to excite ganglionic cells.

Diminution in transmission of nerve impulses in a ganglion may then take place in several ways.

(a) by interference with released acetylcholine.

(b) by preventing the released acetylcholine from acting; the so-called "blocking by competition." All of the ganglionic blocking agents act in this manner.

(c) by causing the ganglion to become the site of a long-lasting depolarization, so that it can no longer give a response to released acetylcholine. This "blocking by depolarization" is observed with nicotine.

In this essay we will consider those synthetic drugs which have come to be accepted as clinical tools in diminishing the transmission of nerve impulses through autonomic ganglia. Among these drugs are, tetra ethyl ammonium compounds (Etamon) and the methonium compounds, pentamethonium (C5) and hexamethonium (C6).

Banthine has a ganglionic blocking activity but this is only manifest at doses fifty times that necessary for eliciting its atropine-like activity. Its blocking effect is short-lived and not utilizable clinically. For these reasons it will not be discussed.

TETRA ETHYL AMMONIUM COMPOUNDS

The introduction of the quaternary ammonium salts into organic chemistry was made in 1849 by August von Hofmann, who proposed a new reaction which would serve to build composite organic ammonium salts from free ammonia. The synthesis of tetra ethyl

*Awarded the Charles E. Frosst Scholarship, 1951.

ammonium salts then became a simple laboratory procedure.

The tetra ethyl ammonium bromide salt ionizes in aequeous solution to form negative bromide ions and positive substituted ammonium ions. The pharmacological response is produced by the positive ions.

Physical Properties

In general the tetra ethyl ammonium salts are solid, deliquescent, ionic substances, readily soluble in water, but insoluble in ether. When strongly heated these salts decompose into tertiary amines and alkyl halides. These salts when combined with alkalis do not decompose, but rather form an equilibrium mixture which contains a fully stable tetra ethyl ammonium hydroxide and free halide ions. Concentrated solutions of the quaternary ammonium salts have a corrosive action and will become contaminated if stored in glass bottles.

Pharmacology

The recognized pharmaceutical name of the tetra ethyl ammonium salts is Etamon; the bromide salt being Etamon bromide. The chief pharmacological action of these compounds was elucidated in 1915 by Burn and Dale (3). These workers found that in dosage of 50mg., Etamon had no effect on the blood pressure of pithed cats. However, in similarly prepared animals, this dose prevented the normal pressor response obtained with 0.5mg. of tetra methyl ammonium salts. From their work they concluded that Etamon acted at the ganglion rather than peripherally. In 1926, Reid Hunt observed that Etamon had no muscarine or atropine activity, nor any "nicotine stimulating" activity, but did possess a nicotine-like paralysing activity.

Further elucidation of the pharmacology of Etamon had to wait until 1945 when G. H. Acheson and his group did extensive experimentation with animals and man (5, 6, 7). In their experiments they noted that, if the superior cervical ganglion and its preganglionic fibres were destroyed, Etamon was ineffective in diminishing the stimulation of the nictatating membrane through the postganglionic fibres of this ganglion. They observed that preganglionic stimulation of the superior cervical ganglion was without effect if this ganglion had first been poisoned with Etamon. Etamon also prevented the contraction of the nictatating membrane usually produced by acetylcholine, but had no effect on the contraction produced by the potassium ion. Lyons et al. (8) studied the activity of Etamon on the cardiac ganglia. They noted that the drug was without effect on the denervated heart, but that in animals in "high vagal tone" (morphine-chloralose anaesthesia) Etamon caused an increase in heart rate, while in animals in "high sympathetic tone" (dial-barbitone anaesthesia) it produced a decrease in heart rate. They also found that intravenous Etamon produced a fall in blood pressure in animals, which could not be obtained if the animal was maintained on continuous drip epinephrine. It was observed, in addition (Lyons (8)), that Etamon reduced gastric acidity and gastric volume in cats.

Following a single intravenous dose of 0.2 - 0.5 Gm. of Etamon, the following sequence of events occurs in man (Lyons (8)).

(1) In 15-20 seconds the patient experiences a metallic taste in the mouth.
(2) In 25-35 seconds, numbness, coldness, and parasthesias of the hands and feet occur, and soon disappear.
(3) After 35 seconds there is incomplete dilation of the pupils and a decreased reaction to light.
(4) The patient feels tired, relaxed and weak.
(5) Diastolic and systolic blood pressures fall in both normal and hypertensive patients. This fall is transitory. Postural hypotension is constantly noted, which may last for 30-60 minutes.
(6) The pulse rate rises to 90-120 per minute.
(7) Sweating stops.
(8) The true digital temperature rises as does the digital blood flow.
(9) Gastric motility and bladder tone are lessened.
(10) The cardiac output rises 20% (Starr method).

A similar sequence of events is noted on intramuscular injection, but the duration of effect is longer; for example, the blood pressure is depressed for twice to three times as long.

Clinical Application

After the preliminary clinical trials, Etamon was utilized in treating hypertension, peripheral vascular disease, aginal pains and gastric disorders.

The work on hypertension can be summarised as follows (Lyons (9)): Etamon produced little or no change in the blood pressure of normal patients; in hypertensive patients a significant fall in blood pressure was noted, which could be prolonged by intramuscular injection. However this drug because of its unpredictability, its side actions, its transitory nature and the postural hypotension it produces has no place in the treatment of hypertension.

Despite the fact that Etamon had proven a disappointment in hypertension, it was used in the diagnosis and treatment of peripheral vascular disease. Berry (10) reported that Etamon improved circulation and ameliorated pain in most patients with peripheral vascular disease. He also believed that it could serve as a useful drug in selecting patients for sympathectomy. Coller (11) verified this work and also reported successes in the treatment of post herpetic neuralgia, causalgia, and anginal pain.

Several workers, among them Nesbit (12), utilized Etamon as a spasmolytic in neurological disorders of the urinary bladder. They reported Etamon effective in reducing spasm, increasing bladder capacity, and reducing the urge to void. Not all neurological bladder conditions responded to this drug, but in those which did, it proved of considerable value.

Etamon is rapidly excreted from the body after intravenous and intramuscular injections. Thirty minutes after an intravenous injection 50% can be recovered in the urine, while after three hours the same amount can be recovered following intramuscular injection. After twenty-four hours all of the drug can be recovered in the urine (Lyons (8)).

Etamon is cold commercially in vials containing 100 mg. per cc. The accepted dosages are:

I/V dose—1–5 cc.—not to exceed 7 mg./kg.

I/M dose—10–12 cc.—not to exceed 20 mg./kg.

It is administered once or twice daily depending on the relief obtained.

This drug received extensive clinical trials but most of the results obtained failed to impress the clinician, for the effects were transitory and the side actions and toxic actions severe enough to contraindicate its wider use.

Side Effects

In addition to the postural hypotension already discussed (page 6), Birchall (13) found that the drug produced a metallic taste in the mouth and numbness and tingling of the extremities, which started as soon as the drug was given and persisted for three minutes. They also noted some degree of ptosis and cycloplegia along with a mydriasis which reached a peak after three minutes, and disappeared only after fifteen minutes. Larger doses were found to produce nasal congestion, muscular weakness, dysarthria, paralysis of laryngeal muscles and even intercostal muscle paralysis. Aas and Blegen (14) reported that Etamon, as well as causing a decreased in diuresis, sometimes accompanied by proteinuria, also produced a reduction in renal plasma flow and filtration rate. From this, they concluded that the drug had deleterious effects on the kidneys, which would limit its usage in patients with impaired renal function. The L.D.50 for the dog was found to be 36 mg./kg., but no specific organ was found to be changed by this toxic dose (Krantz and Carr (37) page 671). In this connection Lyons found no impairment in renal function in dogs to whom toxic doses of Etamon had been given.

Conclusions

From this we are forced to conclude that whereas Etamon has a ganglionic depressant activity which is specific in smaller doses (0.1 –10.0 mg./kg.), in larger doses (40 –400 mg./kg.) it has a peripheral effect. Its activity is transient and its side actions often so severe as to cause alarm. Like other depressants, it produces a postural hypotension. It has been noted to produce a rise in blood pressure in some patients, by evoking a release of adrenalin (or a related substance). This latter effect, though not often reported, could serve to confuse the picture of its true activity (Paton (21)). Its main use at the present time is in the treatment of several types of peripheral vascular disease.

The many obvious usages of an autonomic depressant drug were made evident by this work with Etamon. Despite the fact that this drug was not very useful, workers in the field felt that a depressant which acted like Etamon, without possessing side actions or toxic manifestations, and which possessed a pure ganglionic activity would be a great clinical aid. The discovery of the methonium compounds seemed to fulfill all these requirements.

THE METHONIUM COMPOUNDS

These compounds were first introduced in 1948 by two groups of workers, Barlow and Ing (15) and Paton and Zaimis (16), independently. The former group, in looking for a substitute for d-tubocurare, synthesized many new compounds, which resembled curare in possessing two nitrogen atoms separated by a methylene chain. These compounds were bis-triethyl ammonium dibromides

and bis-trimethyl ammonium dibromides, whose carbon chain lengths were from 2 to 5, and from 7 to 13. These compounds were tested on the phrenic nerve-diaphragm preparation of the rat, and in the rabbit head drop experiment. In the bis-trimethyl series, the curare activity of the C2 chain was twice that of the C4; the C3, C4, C5, chains were feebly active, and the curare activity rose in the C7 to C13 series, being greatest at C8 and falling off at C13. The latter workers in testing the histamine liberating power of octomethylene α, ω,–bis-trimethyl ammonium chloride noted that this compound was effective in blocking nerve muscle transmission.

The synthesis of these compounds is accomplished by refluxing the appropriate diamine hydrochlorides along with methyl iodide and sodium hydroxide, in methanol solution. The sodium chloride formed is removed by filtration, and the methanol is then evaporated, leaving a dry, white residue. The residue is then treated with boiling and later cold acetone, in which the methonium compounds are insoluble, and finally recrystalised from ethyl alcohol solution (Richards (17)).

The compounds became known as methonium, because the term ONIUM is a generic name for cations of ammonium, phosphonium, and sulphonium. Since the compounds are polymethylene salts, they were called "poly"methonium.

The introduction into the field of pharmacology of these newer drugs has opened the field for wider research on the relationship of structure to pharmacological action. Many new compounds have been synthesized, utilizing the known facts of these relationships. One of the newer compounds, known as 9295 (Ciba), has a chemical structure resembling the methonium compounds, in that it is also a type of polymethylene diamine.

It possesses some ganglionic blocking activity, but its usefulness awaits further study. The synthesis of this compound along with the finding that it has an activity like pentamethonium will likely serve as an impetus to further synthesis of compounds whose basic structure contains two pentavalent nitrogen atoms separated by a polymethylene or related chain.

Pharmacology

In discussing the pharmacology of pentamethonium and hexamethonium, it will be best to consider these two drugs together, since they are for the most part used interchangeably. Both drugs are now available commercially in ampoules of 50 mg. in 2.5cc. of normal saline. Pentamethonium is known as Antilusin, and hexamethonium as Hexathide (Allen and Handbury).

The chief action of these drugs is a "blocking by competition" at the synapse of autonomic ganglia. In accomplishing this blocking action, no initial pressor action and no interference with the release of acetylcholine at the ganglia is manifest. Paton and Zaimis (20), working with the nictatating membrane of the cat, showed that the drugs had no action on the membrane itself, since adrenalin was as effective in stimulating the membrane before the administration of the methonium compounds as it was after their administration. They noted that whereas stimulation of postganglionic fibres of the superior cervical

ganglion, innervating the membrane, elicited a response even in the presence of hexa- or pentamethonium, stimulation of the preganglionic fibres in the presence of these compounds was without effect. Finally, they noted that if the superior cervical ganglion was stimulated at the rate of ten per second, 11 millimicrograms of acetylcholine, per cc. of eserinated Locke solution was released. When the experiment was repeated using hexamethonium to depress the ganglion, no stimulation of the nictatating membrane occurred, but the concentration of released acetylcholine was the same as in the control experiment.

Among the most interesting of the experimental findings are the observations that these compounds are not equally active at all ganglia, and also that there is a difference in activity of penta- and hexamethonium at different ganglia. The nature of this difference is not understood, but its practical significance is that further study may result in specific agents for specific ganglia.

The response of the ganglia to the methonium compounds varies with prolonged repetitive stimulation. As the stimulation is maintained, the ganglia became more sensitive to the blocking agents. This led Paton (21) to the hypothesis that the blocking agents are more effective on hypersensitive than on normal ganglia, and accounts for the fact, that these agents will reduce hypertension and ulcer pains (because the involved ganglia are hypersensitive from receiving excessive stimulation) without affecting other "quieter paced" ganglia of the body.

When 1-2mg./Kg. of hexamethonium was injected intravenously into a cat, there was a fall in systolic blood pressure, the magnitude of which depended upon the initial blood pressure. When the initial blood pressure was 160 mm. of mercury, the fall was 60 mm., but when the initial blood pressure was 105 mm. of mercury, the fall was only 10 mm. Further, if the blood pressure was initially less than 100 mm. or, if the animal was pithed, the drug was without effect. It was also shown that neither atropine, neoantergan nor vagotomy had any effect on the response. The fall in blood pressure was activated through a release of sympathetic vascular tone since nicotine, which increases sympathetic vascular tone, was non-effective in the presence of these drugs. In cats the duration of penta- or hexamethonium was 3 to 4 minutes to 20 to 30 minutes, depending on the dose. These drugs also had a cumulative action as seen by the augmentation of effects on repeated similar doses.

Clinical Application

These initial animal experiments were followed by extensive clinical trials in many centres. Arnold and Rosenheim (22), using intravenous pentamethonium (dose—25 - 100 mg.) in normal and hypertensive patients, reported that one minute after injection the pulse rate rose 20 – 30 beats. The blood pressure remained normal in normal patients, unless they stood up, in which case it fell markedly. Vasodilatation accompanied by increase in digital blood flow and digital temperature, ensued after two minutes and was maintained for ninety minutes. In hypertensive patients there was a sharp fall in blood pressure to a steady basal level after two to three minutes, which lasted in some cases

for several hours. Smirk (23) using hexamethonium subcutaneously, and Campbell (24) and Turner (25) using this compound orally both reported favourable results. These workers found that a lowered basal blood pressure could be maintained in hypertensives for many months. Along with the fall in blood pressure there was often relief of the hypertensive symptoms of dizziness, fainting, headache, dyspnoea and ocular disturbances. Some workers also reported regression in the signs of hypertension, viz. diminution of heart size, less papilloedema and better renal function. No electrocardiographic changes were reported. Although hexamethonium and pentamethonium have been used interchangeably in hypertensive therapy, the former is the drug of choice because it produces a more marked effect.

Burt and Graham (26), found that hexa- and pentamethonium both produced an increased skin blood flow, the effect being greater in the lower extremities, where the duration was 35-60 minutes, than in the upper extremities, where the duration was only 2-10 minutes. Sweating was diminished and in some cases abolished by these drugs, but again the effect was more marked in the lower extremities. They also noted that both the drugs produced a slight mydriasis.

The production of hypotension was utilized by Enderby (27) (28) and Lewis (29) to minimise blood loss in surgery. These workers found that they could maintain a controlled hypotension of 55–80 mm. of mercury in 85% of their cases. Lewis reported that hexamethonium had a more constant action in reducing blood pressure than pentamethonium. He found that the iodide of hexamethonium was more effective than the bromide, while in using pentamethonium the iodide and bromide were equally effective. He also found that less anesthetic was needed when these drugs were used, and he postulated that the lowered blood pressure might cause lowered tissue metabolism, which in turn would account for the lessened amount of anaesthetic needed to narcotize the individual cells.

The specificity of the ganglionic blocking activity of these compounds resulted in their employment in studies on gastric secretion and motility. Kay and Smith (30) (31) (32) reported that hexamethonium administered both intramuscularly and orally produced a decrease in secretion with achlorhydria, lasting 2–3 hours. It also caused a reduction in the volume and acidity of night secretion, gave prolonged inhibition of gastric motility, and relief from pain and hunger symptoms lasting up to five hours in patients with ulcers. It prevented the true insulin gastric secretion response but had no effect on the histamine response. This is further proof of its activity at autonomic ganglia. Douthwaite (33) repeated this work using radiological analysis of gastric motility and noted that the methoniums lessened gastric emptying time, gastric peristalsis and small bowel peristalsis. The results of this work form the basis for the treatment of peptic ulcers with the methonium salts.

In Europe, pentamethonium was utilised as an antagonist of decamethonium for, it had been noted (Organe et al (34)) that if pentamethonium was previously administered in a dose of 10–100 times that of decamethonium, it abolished the paralysis produced by de-

camethonium. When given following the decamethonium, it diminished the paralysis, hastening recovery. The utilization of pentamethonium as an antagonist and antidote of decamethonium is not recognized in North America owing to the side effects of this compound.

Side Effects

The side effects of the methonium compounds are the main obstacles to their wider usage. Both the drugs produce a postural hypotension which outlasts their activity in lowering blood pressure. In some cases this is so severe that dizziness and syncope result, making it necessary for patients to remain supine for several hours after receiving the drug. This postural hypotension is prevented by the patient exercising his leg muscles, but is made worse by the patient standing still. This could mean that the methonium compounds produce a relaxation of venous tone which is overcome by muscular action. Besides this side effect, bromism and iodism have been known to occur in some patients (Lockett /35). This could be avoided by using salts other than bromides and iodides. Lockett also found that 17-ketosteroid excretion fell to one-half in patients on hexamethonium, but he felt that this was in some way related to the bromide ion. The drugs seem contraindicated in recent coronary infarcts and in cerebral thrombosis.

Metabolism

The metabolism of the methonium compounds has been worked out by Milne and Oleesky (36). They reported that 60-70% of an intravenous dose of hexamethonium was excreted unchanged in the rabbit, and 100% of an intramuscular dose excreted without change in the human. Oral doses were poorly and variably absorbed.

Dosage

The dose and mode of administration of these drugs is not as yet settled but most workers agree on the following:

Oral dose:	500-1000 mg. of pentamethonium, repeated every four to six hours.
	250–500 mg. of hexamethonium, repeated every four to six hours.
I/M dose:	25–150 mg. every two to six hours, for both compounds.
I/V dose:	20–50 mg. every three to six hours, for both compounds.
S.C. dose:	50–250 mg. three times a day, for both compounds.

The dose varies with the condition treated, being higher for peptic ulcer and lower for producing hypotension.

CONCLUSION

In summary, the methonium compounds, unlike Etamon, are specific autonomic ganglionic blockers with no side action on smooth muscle or on the myoneural junction, and no adrenolytic effect. They possess none of the undesirable side effects of Etamon, such as tingling of the extremities, metallic taste in the mouth, mydriasis, cycloplegia or paralysis of laryngeal muscles. They are more effective than Etamon in smaller doses (1/10–1/20 the dose) and their duration of activity is much greater. Their only undesirable effect, also found with Etamon, is that they produce a severe postural hypotension

which in some cases makes out-patient care very difficult. Their main applications at the present time are in surgical maneuvers where bloodless fields are desired, in peptic ulcer patients, and in severe hospitalised hypertensives.

The most important physiological aspect of autonomic depressants is that they afford a mechanism for the study of autonomic activity. It is possible that these drugs will allow us to examine how far abnormal activity in normal and in abnormal organs originates in the central nervous system, and how far it is mediated by the autonomic system.

The problem that now faces the research worker in this field is the preparation of a compound which could lessen the activity of "hypersensitive" ganglia but still allow normal function to be carried out. The postural hypotension which is an accompaniment of any reduction in blood pressure poses the greatest problem in accomplishing this end. The ideal drug for treating hypertension would be a compound active orally, which would reduce hypertension for three to six hours without producing as severe a postural hypotension as seen with the methoniums. This new drug if it fulfilled these conditions would simplify out-patient care. It is possible that any ganglionic blocking agent which is effective in reducing blood pressure, must also affect vascular tone to the extent that postural hypotension becomes inevitable. If this is true, it might be that a compound could be found which, when administered in conjunction with the ganglionic blocking agent, would alleviate the hypertension without causing as pronounced a postural hypontension as noted with the blocking agent alone.

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SIGNS AND SYNDROMES

As a sequel to the "proper names quiz" appearing in an earlier edition of THIS JOURNAL, we present a test in which the reader is given twenty different signs which bear their originators' names. These signs are important (although not necessarily pathognomonic) in the diagnosis of certain syndromes, and should suggest to the reader either specific disease entities or types of pathology. For example, Moebius' sign, (failure of convergence), is one of the eye signs in *hyperthyroidism;* again, Macewen's sign, (the cracked-pot sound heard on percussing the skull), should suggest to the student *hydrocephalus.* The former condition is a specific disease; the latter, a pathological condition found in a number of illnesses. Most of the signs given below are somewhat easier than the two examples given.

1. Chvostek's sign
2. Murphy's sign
3. Cullen's sign
4. Kernik's sign
5. Carman's sign
6. Rovsing's sign
7. Hegar's sign
8. von Graefe's sign
9. Courvoisier's sign
10. Duroziez's sign
11. Wimberger's sign
12. Queckenstedt's sign
13. Pardee's sign
14. Brudzinski's sign
15. Trousseau's sign
16. Boas' sign
17. Chadwick's sign
18. Trendelenberg's sign
19. Stellwag's sign
20. Romberg's sign

Answers on Page 174

DIABETES IN PREGNANCY

G. H. ECKERT, 5T2 and A. J. SMITH, 5T2

INTRODUCTION

Prior to the advent of insulin the great majority of diabetic women were sterile but now with better understanding of insulin therapy, the number of juvenile diabetics living who become pregnant has increased steadily. The underlying cause of the infertility in diabetics during the pre-insulin era was probably due to a number of factors, most of which are poorly understood.

Structural changes have been observed in the reproductive organs of diabetics by a number of authors, including the disappearance of Graafian follicles and uterine atrophy. Amenorrhea was common in diabetics of that period. This evidence of ovarian dysfunction suggests the infertility was probably due to hyper or hypofunction of the anterior pituitary gland. In the pre-insulin era the restricted diets of diabetics may also have been a factor in infertility. A vascular component may also play a part.

When diabetic women did occasionally become pregnant some 25% of the mothers and about 50% of the infants died. This experience of the pre-insulin era is of great clinical importance because it shows that untreated diabetes and pregnancy are basically incompatible.

The authors would like to take this opportunity to acknowledge their indebtedness to Dr. Priscilla White of Boston for making available to them her reports and for permission to publish the figures in this Journal.

INCIDENCE

The frequency of pregnancy complicated by diabetes is reported as between 1:500 or 1:1000 pregnancies. When diabetes is encountered in pregnancy the chances are greatly in favor of it being met in older women in whom hypertension may also be a factor.

This report consists of a study of a series presented by White in 1951 comprising 597 cases of pregnancy in known diabetics treated in the Joslin Clinic between July 1, 1936 and May 15, 1951. 525 of these cases had viable infants of whom 439 survived and 80 died, i.e. 16% fetal mortality.

60.5% of these patients had their age of onset of diabetes under 20 years of age.

Table I

Duration of diabetes in years at time of delivery (525 cases).

Years duration	*No. of Patients*
25—29	10
20—24	35
15—19	90
10—14	120
5—9	130
1—4	140

The distribution of these 525 cases is shown in their respective classes according to White's classification of Diabetes in Pregnancy, i.e. a pregnancy severity grading devised in 1948 in the Joslin Clinic.

The designation is alphabetical from A—F and depends on:

1. Age of patient at the onset of diabetes.

2. Duration of the diabetes.
3. Presence or absence of vascular lesions.

Classification of Diabetes in Pregnancy (White)

Class A: Includes sub-clinical diabetics, those in whom the diagnosis is based upon the Glucose Tolerance Test which deviates but slightly from normal. These patients require no insulin therapy and very little dietary regulation.

Class B: Includes diabetics in whom the onset of diabetes occurred after the age of 20 years, in whom the duration is less than 10 years and who have no vascular lesions.

Class C: Includes patients in whom the onset of diabetes occurred between the ages of 10—19 years, or whose duration is relatively long—between 10—19 years and who show no vascular lesions.

Class D: Includes the really young at onset, under 10 years of age or those whose duration is more than 20 years or those with calcification of the leg vessels or with retinitis.

Class E: Includes a small group of patients with arteriosclerosis demonstrable in the pelvic vessels.

Class F: All patients with diabetic vascular nephritis, i.e. Kimmelstiel-Wilson's Disease, as evidenced by hypertensive cardiovascular disease, anasarca, proteinuria.

The number of patients in each of the various classes is seen in Table II.

Table II

Number of patients in respective classes

Class	*No. of Patients*
A	25
B	144
C	187
D	121
E	36
F	12

Thus nearly 70% of these patients fall into classes C D E F and only 30% in A and B. In this respect this series differs markedly from many hospitals where 80-90% are in class A and B and only 10-20% in C D E F.

Ries in 1950 reported a series of 53 patients with 9 of whom had had diabetes over 10 years.

Givens in 1950 reported a group of 106 patients only 10 of whom had had diabetes for 10 years or more.

Thus Dr. White's series cannot be compared to any other reported series and until a classification such as outlined previous is understood and adopted comparisons of statistical reports are impossible.

DIAGNOSIS

Before proceeding further I would like to point out that the presence of sugar in the urine of a pregnant woman many indicate one of three conditions or any combination of them.

1. Lactosuria
2. Renal Glycosuria
3. Diabetes Mellitus

Lactosuria seldom occurs normally during pregnancy, under normal conditions of lactation but is present in a

considerable proportion of women during the period of lactation. It is seen in only 1-2% of gravidae prior to the last six weeks but at that time its incidence increases to 7-8%. Lactose can be readily identified by standard laboratory tests.

Glycosuria occurs in from 10-15% of all normal pregnant women, particularly in the latter months and more frequently in primipara than in multipara. The fasting blood sugar level remains within normal limits during this period. This non-hyperglycemic glycosuria of pregnancy is ascribed by some to a diminution in the renal threshold level for glucose. Others believe it to be due to an actual decrease in glucose tolerance resulting perhaps from a state of physiological hyperpituitarism which may be present at this time.

Diabetes Mellitus gives a characteristic glucose tolerance curve.

THE PROBLEMS

There are four main abnormalities in Diabetic Pregnancies.

1. Maternal
2. Obstetrical
3. Chemical
4. Fetal

1. Maternal:

A. vascular disease

Vascular disease is inevitable in young patients with diabetes of longer duration than 15 years. Arteriolar sclerosis as well as atherosclerosis is found and affects the eyes and kidneys. Nephritis replaces sepsis and is now replacing coma as a cause of death in young diabetics.

B. hypo-ovarianism

Hypo-ovarianism is indicated by increased serum level of FSH, by amenorrheas and by metorrhagias. Pathologically atrophy of the ovary with poor follicular development can be seen.

2. Obstetrical:

A. The incidence of spontaneous abortion and premature delivery is increased and occurs especially in those patients with vascular disease. Thus among women whose infants died in utero, 75% had some evidence of vascular disease. It is rare for intrauterine death to occur after the 33rd week in the absence of one of the complications such as pre-eclampsia, hydramnios, albuminuria without hypertension. On the other hand death of the fetus is likely to occur within a few days after any of these complications have developed.

B. The incidence of pre-eclamptic toxemia is increased.

C. Hydramnios is more common.

D. Increased incidence of breech presentation.

3. Chemical:

A. changes in sugar tolerance

1. Sugar tolerance is often diminished, i.e. more insulin is required due presumably to increased activity of the anterior pituitary gland.

2. Sugar tolerance is sometimes increased, i.e. less insulin is required due either to the activity of fetal pancreas or to other factors.

3. Vomiting with loss of unknown amounts of carbohydrate food may simulate raised sugar tolerance, may provoke acidosis and in any event confuse the dietary picture.

4. During labor the muscular exertion entailed may so deplete the glycogen re-

serve that sharp alterations in carbohydrate and insulin requirements ensue.

5. A gain in sugar tolerance often occurs after delivery and hypoglycemia in the puerperium is very common. It may be associated with sudden and extreme vacillations in blood sugar due apparently to reconversion of bodily mechanisms to their non-pregnant states. Lactation with conversion of certain amounts of blood glucose into lactose may also play a role. Puerperal infection, even though mild, may precipitate acidosis and coma with great rapidity.

B. INCREASED TENDENCY TO KETOSIS

The elevated B M R in pregnancy increases the tendency towards acidosis and is facilitated by a reduced supply of glycogen, a changing need for insulin, hyperemesis and nutritional deficiencies, especially B complex.

Beginning about the second month of pregnancy there is a gradual progressive decrease in total serum base, plasma CO2 C.P. alveolar CO2 tension and plasma bicarbonate. The plasma pH is usually within normal limits.

There is still much controversy over the interpretation of these observations —the point being whether the fall in plasma bicarbonate is brought about by primary CO2 deficit or by a primary alkali deficit.

C. WATER RETENTION

As shown by increased gain in weight, visible maternal edema and by hydramnios.

D. HORMONAL IMBALANCE

As shown by fall in pregnandiol, serum estrogens and increased chorionic gonadotrophin. This problem is discussed further under Therapy.

4. FETAL:

A. PHYSICAL

1. Increased birth weight in 80%. The size of the infant is due to obesity, edema and splanchomegaly seen especially in liver, spleen and heart.

2. A high incidence of congenital defects in tissue of mesenchymal origin. It has been suggested that paternal diabetes may also have the same effect.

B. CHEMICAL

On the first post-natal day, respiratory, sugar metabolism and temperature regulatory difficulties are encountered.

C. PATHOLOGICAL

Pathological changes are almost diagnostic of maternal diabetes: large liver, spleen and heart; excessive hemopoiesis of liver and spleen; islet hyperplasia in the pancreas.

The background for normal pregnancy includes normal function and structure of the pituitary, ovaries, uterus, placenta, liver, enzyme systems and cardio-vascular system. However in the diabetic the kidney shows latent vascular disease; the enzyme system is under suspicion; the function of the liver can be altered by abnormal deposition of glycogen and fat; the uterus and ovaries are those of suspicion; the placenta fails in its production of sex hormones and without the inhibiting influence of estrogen and progesterone, pituitary over-activity may occur.

TREATMENT

Treatment of diabetes in pregnancy resolves itself into two problems (1) preserving the life of the mother and preventing injurious complications to her as a result of the pregnancy (2) preserving the life of the fetus and new-

born child. Today almost all maternal deaths in pregnant diabetics are due to neglect. Infant mortality on the other hand averages about 25% of those fetuses which reach a viable stage, fetal death in utero and neonatal death being greatly increased in these infants. The greatest problem in treatment to-day is thus how to increase fetal survival. The largest continuous series of treatments of these patients has been done by Dr. Priscilla White of Boston and it is proposed to give an outline of her methods of treatment and the results obtained while introducing at the same time the ideas of other competent investigators.

Outline of Treatment:

It is generally agreed that the close co-operation of physician, obstetrician and pediatrician is essential for the satisfactory termination of pregnancy and for the survival of the newborn baby. A brief summary of the treatment involved is outlined below.

MEDICAL

1. Control diabetes.
2. Restrict sodium retention—diet-salt free—high protein—ammonium chloride—mercury.
3. Sex hormone therapy—dosage according to diabetic classification and weeks of pregnancy.

OBSTETRICAL

1. Prenatal care—weekly.
2. Early hospitalization.
3. Early recognition — toxemia — hydramnios—fetal distress.
4. Avoidance of intrauterine death by delivery at or before 37 weeks —according to classification and complications.
5. Pediatric care.

Some authors feel that diabetic patients contemplating pregnancy should undergo an evaluation before pregnancy is established. (2) In particular, juvenile diabetics are known to have premature vascular sclerotic changes and it is felt that they should be advised against pregnancy if any of the following are present:

(a) calcification of iliac vessels (X-ray).
(b) retinopathies.
(c) coronary heart disease.
(d) nephritis (intercapillary glomerulosclerosis, i.e. Kimmelsteil-Wilson Disease).

However some investigators feel that the first two complications listed are not necessarily absolute contra indications to pregnancy. Before 1936 very few juvenile diabetics became pregnant. To-day over 60% of a series of 525 presented by White are in this class and hence present a real medical and obstetrical problem.

Prenatal Care:

Patients are encouraged to report as soon as pregnancy occurs and weekly examinations are carried out thereafter in the hope of revealing any early complications.

A suitable diet is prescribed and most authors feel that 30 calories per kilogram are adequate for the well controlled diabetic. This should consist of 2 grams of protein per kilogram; 180 to 250 grams of carbohydrates; the remaining calories being made up with fat. Thin patients are given slightly higher, and obese patients are given slightly lower caloric intakes per kilogram. Nausea and vomiting of the first trimester are treated with small frequent

meals and crystalline insulin until the patient gets over this phase.

Insulin requirements are regulated and a single dose of N.P.H. insulin mixed with crystalline insulin controls the majority of these patients. In patients whose renal threshold for glucose is low multiple doses are necessary and are given before each meal. Reis (2) has outlined a criterion of good insulin dosage as being one that:

(a) avoids acetonuria.
(b) lowers the level of blood carbohydrate.
(c) reduces glycosuria.
(d) leaves patient with a sense of well being, which is best done with a slight glycosuria.

Ketosis is harmful to the fetus particularly in the second trimester and White found that in 10% of viable infants who later died, death was associated with a recent bout of acidosis.

Patients are taught to test their own urine for sugar and for acetone.

Weekly retinal examinations are done to determine the development or extent of retinopathies. At the same time a determination of capillary fragility is done and if either condition is present Rutin is prescribed. This treatment is not accredited by many investigators. The high protein diet and chemical control of the diabetes mellitus helps prevent these ocular and vascular changes.

Weekly N.P.N., quantitative albumin and examination of urinary sediment is done to detect any change in kidney function. Infections are detected early and treated vigorously to avoid the rapid progression of diabetic nephritis which occurs in the presence of infection.

Iron salts are administered on the basis of weekly hemoglobin tests.

Vitamin B is prescribed in excess as it is felt that the gastric neuropathies of diabetes mellitus cause these patients to be deficient in the B vitamins.

To prevent or correct the appearance of oedema and hydramnios the patient is placed on a low salt, high protein diet. Ammonium chloride 4–12 Gm/day is prescribed for all patients. If hydramnios occurs which fails to respond to increased ammonium chloride it is treated with weekly 1cc. I.M. doses of mercuhydrin as long as there is no evidence of vascular nephritis.

Hormonal Therapy

It is felt by Dr. White's group that if the level of serum chorionic gonadotrophin rises and that of serum estrogen and urinary pregnandiol fall that there is a coincident rise in fetal mortality. Thus by following the chorionic gonadotrophin levels of their patients they have been able to predict the onset of fetal difficulties and obstetrical abnormalities in a number of their cases. On the basis of these hormonal changes a programme of hormonal therapy for the pregnant diabetic has been worked out by White and her fellow workers, the programme to commence as soon as pregnancy is diagnosed. Intramuscular injections of stilbestrol and proluton in equal amounts are administered daily, generally by the husband. The dosage varies with the week of pregnancy and with the severity of the diabetes as determined by the diabetic grading system used. (*See Table III*)

Results

From July 1, 1936 to May 15, 1951

TABLE III

Basic Plan of Daily Hormonal Treatment by Class.
Dosage of I.M. Stilbestrol and Proluton in milligrams of each.

Week of Pregnancy	A	B	C	D	E	F
0 – 10	0	5	5	10	25	25
10 – 20	0	5	5	10	25	25
20 – 24	0	10	10	15	50	50
24 – 28	0	15	15	25	75	75
28 – 32	0	25	25	50	100	100
32 –	0	50	50	75	125	125

Therapy Regulation Based Upon:
1. Weekly serum gonadotrophin and urinary pregnonediol (glucuronidate) levels.
2. Clinical evidence of disturbed water balance or pre-eclampsia.

there have been a total of 597 diabetic obstetrical patients treated by the White group. The results are tabulated below. Of the 525 viable cases, viability meaning an infant of 2 lbs. or over, only 47 of the mothers showed a normal hormonal balance all through pregnancy and hence received no hormonal therapy. The remaining 478 women with abnormal hormonal levels were divided into a control group of 98 who received no hormonal therapy and a group of 380 who were given hormonal therapy in an attempt to correct their hormonal imbalance.

Total cases	597	
Spontaneous abortion	54	
Therapeutic abortion..	18	
Total viable cases	525	
Fatals	86	(16.5%)
Live births	439	(83.5%)
Abnormal treated	380	
Fetal mortality	37	(10%)
Abnormal untreated	98	
Fetal mortality	47	(48%)
Normal—no treatment	47	

TABLE IV

Outcome by Class and Hormonal Treatment—White's Series

		A	B	C	D	E	F
	%	%	%	%	%	%	%
Live Births	Treated	100	79	82	78	46	50
	Untreated	100	67	48	32	13	..
Stillbirths and Neonatal Deaths	Treated	0	11	10	13	40	31
	Untreated	0	23	28	32	13	..
Spontaneous Abortion	Treated	0	10	8	9	14	19
	Untreated	0	10	24	36	74	..

702 Cases—Total Experience Joslin Clinic 1924–1951.

Fetal mortality 2 (5%)
Duration of diabetes:
Under 10 years 270
Over 10 years 255

These results indicate an appreciable increase in fetal survival in the abnormal treated group—90% as opposed to the abnormal untreated group—52%. Further there is an increase in fetal survival even in the very severe classes of diabetic women treated. (*See Table IV.*) The increase in fetal survival is due to decreases in stillbirths, neonatal deaths, and spontaneous abortions. Further the incidence of toxemia of pregnancy which in diabetic women rises to 25–50%, has been reduced by hormonal therapy to the average found in the normal population. Also such obstetrical abnormalities as spontaneous abortion and premature delivery were significantly reduced in the hormone treated group as compared to the untreated control group.

The only constant variation of treatment in the entire group since 1936 has been the administration or not of hormonal therapy, otherwise, as prenatal and postnatal improvements in obstetrical care have been discovered they have been applied to every patient in the entire group. Thus it is felt that hormonal therapy has played a great part in reducing fetal mortality in the treated group to 10% despite the fact that 70% of the group fell into the severe C, D, E and F classification. There are no groups of comparable severity reported in the literature and it would appear that hormonal therapy has a place in the prenatal care of the pregnant diabetic unless an equivalent series with equivalent results can be produced without recourse to hormonal therapy.

Early Hospitalization

Early hospitalization is essential for the adequate treatment of the pregnant diabetic woman. In these women complications of pregnancy are common particularly after the 30th week, i.e. intrauterine death, hydramnios, albuminuria without hypertension, toxemia, rise of N.P.N., spontaneous premature labour and X-ray halo about the fetal body or head. Intrauterine death occurs between weeks 33 to 40 with a peak at 36 and it is felt that all patients should be admitted to hospital in the 34th week of pregnancy or earlier if complications develop. The patient remains in hospital until delivery occurs. The sudden onset of complications like toxemia, hydramnios and fetal distress make it hazardous to leave the patients out of hospital any longer. The women most susceptible to intrauterine death are those with vascular damage and in this series it was found that 75% of such deaths were associated with vascular damage in the mother. Intrauterine death is rare after the 33rd week unless preeclampsia, hydramnios, albuminuria and other complications arise. But if these complications do occur the fetus may die within a few days of onset of the complicating factor.

Early Delivery

The obstetrician is faced with the problem of deciding how early to deliver the fetus before intrauterine death occurs and at the same time how to prevent the risks of premature delivery to the baby. The time of delivery is considered with respect to the diabetic

classification of the patient and to the presence or absence of complications. Thus mild diabetics under good control are induced when the cervix is ripe, the indications of which are (1) head below the ischial spines (2) cervix one finger dilated (3) cervical canal less than one centimetre long. Moderately severe diabetics under good control (groups C, D, E) are delivered by caesarian between the 36th and 37th week. Severe complicated cases with toxemia, hydramnios, albuminuria and fetal halo should be delivered by caesarian as soon as the baby is viable if possible carrying the pregnancy to the 34th week. As there were many complicating factors in this series most of the deliveries were carried out from the 33rd to 37th week.

Vaginal Delivery

Pelvic delivery was not complicated by abnormally large babies in the hormone treated group, the hormones apparently limited the growth of the fetus to a normal size. This was not so in the untreated patients. In pelvic deliveries it is wise to keep sedation at a minimum and spinal anesthesia is considered the vehicle of choice.

Caesarian Section

The indications for caesarian section have increased since the introduction of antibiotics and the transperitoneal low segment operation. Maternal mortality is less than 0.5% and earlier caesarian is a factor in keeping fetal mortality down. To-day some investigators feel "that early induction of labour and prematurity need not increase the neonatal death rate" (3). If this is so any objections to early delivery on the grounds that the premature baby will only suffer neonatal death are removed.

Method:

1. Continuous spinal anesthesia without preliminary medication.
2. An I.V. solution of 10% glucose in distilled water is started half an hour preoperatively.
3. The last dose of insulin is given 24 hours prior to delivery. If crystalline insulin is being used it should not be given within three hours of delivery. Insulin is withheld on the day of the delivery until the operation is over in order to prevent hypoglycemia in the mother and newborn baby.

Pediatric Care

The care of the newborn infant is designed to prevent respiratory difficulties and the problems of hypoglycemia and congestive failure are not felt to be important. Thus pediatric care in this series consists of:

1. postural drainage.
2. aspiration of upper respiratory tract and stomach.
3. oxygen.
4. incubation for 5 days.
5. postponement of feeding for 48 hours to dehydrate the baby.

In the series by Reis (2) the baby no matter what its size was treated as a premature, in an incubator with oxygen. The postnatal problems which were felt to be important in this series were anoxia, lethargy and hypoglycemia. Thus the airways were meticulously cleared, the baby was frequently stimulated to overcome lethargy and the baby was fed soon after birth to overcome hypoglycemia. Eastman advocates the

injection of 5cc. of 10% glucose into each buttock immediately after birth and this is repeated or not depending on the behaviour of the baby, the feedings being given and on the blood sugar level. He also gives 10cc. of glucose solution by mouth or I.M. whenever twitching, convulsive movements or cyanosis indicates the development of hypoglycemia. Also during the first three days of life sugar solution is given by mouth or I.V. at frequent intervals because "It can do no harm" (1).

Post Partum Care

The post partum care of the diabetic mother as far as White's series was concerned presented few complicating factors. Control of the diabetes mellitus is the main problem as wide fluctuations in sugar tolerance occur immediately post partum. Among possible causes of this phenomenon are:

1. changes in endocrine and metabolic function.
2. slight puerperal infection.
3. conversion of some blood glucose to lactose.
4. sudden withdrawal of the fetal pancreas—this is a very unlikely cause.

It should be understood that pregnancy will not permanently aggravate diabetes mellitus if it is well controlled throughout pregnancy. Thus the treatment of post partum diabetes with crystalline insulin 3 or 4 times a day will soon bring the patient to a well controlled state once again.

Therapeutic Abortion

Finally the indications for therapeutic abortions must be considered. The White group stress the point that the severity of the diabetes as judged by the amount of insulin needed to control it is definitely not an indication for therapeutic abortion. Rather the degree of vascular damage which has occurred is the important factor and this is manifest as:

(a) diabetic nephritis.
(b) retinitis proliferans with some vision still remaining.
(c) advanced or progressive retinitis.

Only on the basis of these three factors is therapeutic abortion carried out.

SUMMARY

In the preparation of this article on the problems of diabetes in pregnancy, the views of Dr. Priscilla White of the Joslin Clinic, Boston, have been prominently featured. The views of other investigators have been introduced where possible.

ACKNOWLEDGMENT

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CARCINOMA OF THE STOMACH

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At Present the cure-rate for carcinoma of the stomach is the worst of any malignant disease. This is true, simply because it is a silent, stealthy killer, which has thus far defied all attempts at early recognition. It is the thief-in-the-night of malignancies, which without warning, swiftly overwhelms its victim, and robs him of health and life.

INCIDENCE:

Gastric carcinoma is alarmingly common. It comprises five per cent of all cancers, and accounts for twenty per cent of all deaths due to malignant disease.

Males are more susceptible than females in the ratio of three to one; indeed it is the commonest cancer found in men.

The disease occurs from age twenty-one to seventy, but is most frequently seen in the fifth and sixth decades.

The incidence of stomach cancer in Pernicious Anemia patients is noteworthy. In these cases, it is twenty times more common than in the general population.

ETIOLOGY:

The etiology of this disease is unknown. Chronic gastritis due to any cause has long been considered a factor since it frequently precedes, and is often associated with gastric cancer. However, Fenwick et al. have shown that similar atrophic changes occur in the stomach when carcinoma of other organs in the body is present.

Most authors suggest that five per cent of chronic gastric ulcers become carcinomatous, yet Abrahamson and Hinton followed a large series of benign ulcers patients for one to nineteen years, yet failed to observe a single case in which this transformation could be proved.

We have already referred to the frequent appearance of gastric carcinoma on the atrophic mucosa of P.A. patients.

PATHOLOGY:

The site of election in the vast majority of gastric carcinomas is the prepyloric area (60–70%), or along the lesser curvature (20%). The cardia or fundus are involved only rarely, and the greater curvature, more rarely still.

Kauffman describes a histological classification of cancers of the stomach, but a more common and useful grouping is the anatomical one based on the gross appearance of the neoplasm.

Four characteristic forms are differentiated:

1. Ulcerocancer
2. Papillary Adenocarcinoma
3. Scirrhous Carcinoma
   a) local b) diffuse
4. Mucoid or Colloid Carcinoma.

1) Ulcerocancer

This type is the common form of gastric carcinoma and is usually found in the prepylorus. It appears as a raised, localized thickening of the stomach wall which ulcerates producing pain, hemorrhage, and giving rise to infection. Microscopically it is characterized by solid, irregular masses or columns, of atypical

epithelial cells embedded in a dense fibrous stroma. Ulcerocancer tends to infiltrate the submucosa, and may form small nodules on the serosal surface.

2) Papillary Adenocarcinoma

This tumor occurs in the prepyloric area as a friable, cauliflower-like mass, which if large, may cause obstruction of the pylorus. Fragments of the soft, fungating growth frequently become necrotic and crumble away, thus causing hemorrhage and infection.

Microscopically the adenocarcinoma is composed of atypical glands lined by cells with large, hyperchromatic nuclei. The glands may be seen to penetrate deeply into the gastric wall, even to the serosal surface.

3) Scirrhous Carcinoma

Two types of scirrhous carcinoma of the stomach can be recognized:

a) local type

This neoplasm forms a localized induration of the gastic wall in the juxtapyloric area. As the growth progresses, a dense sclerotic ring is formed which constricts the lumen of the stomach causing stenosis, and so giving rise to symptoms and signs of obstruction. Dilatation occurs proximal to the lesion.

b) diffuse scirrhous carcinoma

This is an extensive infiltration of the stomach wall from cardia to pylorus, in which the wall becomes thickened and indurated, and the whole organ converted into a shrunken, sclerotic "leather-bottle." The stomach is greatly reduced in size, and contains only one-tenth of its normal volume. The cut surface is very thick and presents a characteristic "woven-linen" appearance, which when observed by Briton in 1854, prompted him to designate the disease "linitis plastica."

Microscopically, scirrhous carcinoma of the stomach is anaplastic in type, with very little evidences of glandular formation. The anaplastic cells are found singly or in small groups, deeply embedded in a dense stroma of scar-like fibrous tissue.

SPREAD

Spread occurs early in the disease and takes place by direct extension, by lymph, and blood stream. In addition, if the tumour penetrates the stomach wall and so gains access to the peritoneal cavity, spread may occur by implantation. Any of the neighbouring organs may be involved: the liver, pancreas regional lymph nodes, transverse colon, oesophagus, omentum, etc. Distant metastases may be found in lungs, bones, brain, kidneys, peritoneum, ovaries.

SYMPTOMS

Gastric carcinoma is treacherously symptomless. A patient may harbour a cancerous lesion for months, yet suffer only such trivial complaints as fatigue, weakness, anorexia or mild indigestion. It is not surprising, therefore, that in the overwhelming majority of instances only the advanced cases of gastric malignancy are diagnosed. Accordingly, the symptoms most consistently presented by such patients are: (Lawton et al.) weight loss (74%), epigastric pain (72%), vomiting (53%), fullness after meals, indigestion, constipation, tarry stools, dysphagia, tumour, diarrhea, and more rarely, hemorrhage, anemia and jaundice. None of these is invariably present in gastric cancer. Some occur

early in one patient, late in another, and any, or none of the above may be present in an isolated case. Obviously, symptomatology in gastric malignancy cannot be considered useful for diagnostic purposes.

DIAGNOSIS

Any patient in the cancer age group with a history of chronic fatigue, weakness, mild indigestion or similar minor complaint, and who now is suffering from weight loss, or pain, or vomiting, or notices epigastric fullness after meals, must be assumed to have cancer of the stomach until proved otherwise.

Similarly, any ulcer in the prepyloric region of an older patient must be seriously suspected of malignancy and investigated as such.

Investigation is carried out by physical examination, blood and stool examinations, X-ray, gastric acidity tests, gastroscopic examination, cytological examination and laparotomy.

PHYSICAL EXAMINATION

Physical examination in gastric cancer patients is variable. The patient may appear normal, or he may be pale (or even jaundiced), underweight, and even cachectic.

Abdominal examination may reveal no abnormalities, or may uncover a stony-hard irregular mass in the epigastrium. The liver may be enlarged due to secondaries; abdominal fluid may be present. Careful digital examination may reveal a rectal shelf.

The left supraclavicular lymph node (sentinel node) may be palpable.

BLOOD:

In 30 per cent of patients with gastric cancer, the blood Haemoglobin estimation is below 75 per cent. In three to five percent, there is an associated pernicious anemia.

STOOLS:

Thirteen per cent of patients with gastric cancer will have stools tarry in colour, and in 95 per cent, blood can be demonstrated by Benzidine test.

X-RAY:

X-ray examination after a barium meal will reveal 90-92 per cent of stomach malignancies. The radiological diagnosis of cancer of the stomach is based on:

1) Filling defect which persists with changes in patient's position.
2) Alteration in normal pyloric function causing increased or decreased emptying time.
3) Absence of peristalsis in a limited segment of gastric wall.

Any surface fraying of gastric mucosa, any protrusions of the mucosa, or any interruption in the peristaltic waves passing down stomach wall are signs of a pathological process, and should be viewed with suspicion.

GASTRIC ACIDITY:

The estimation of gastric acidity has only limited value since fifty per cent of all people over the age of fifty have some reduction. However, 84-87 per cent of cases have achlorhydria, or hypochlorhydria, indicating reduced function of the gastric mucosa.

GASTROSCOPE:

Visualization of the lesion, and the taking of a biopsy if possible, is the object of gastroscopic examination, and should be carried out in all questionable

cases. A negative biopsy report must not be relied on too heavily, but should be carefully considered in the light of other findings.

CYTOLOGY:

The microscopic examination for malignant cell nuclei in gastric washings or vomitus is not of great value. Even Papanicolaou, originator of this diagnostic procedure, reports accuracy of only 33-35 per cent.

LAPAROTOMY:

Laparotomy, with the possibility of extensive resection in mind, is performed in all diagnosed cases, unless there is obvious evidence of metastases already present. It is important to realize that even with the stomach opened and the tumor in full view, in 15 per cent of cases it is impossible to tell by inspection and palpation whether the lesion is malignant or benign.

TREATMENT

Treatment is by surgical resection of the diseased areas. Unfortunately however, a large proportion of patients admitted to hospital are doomed to die without even undergoing curative surgery. This is the most distressing feature of this disease, and accounts for its very low cure-rate. Due to difficulties in diagnosis caused by its remarkable insidiousness, and to delays caused by both patient and physician, a case of gastric cancer seldom comes to operation early—but often comes too late!

Thirty per cent of diagnosed carcinomas of the stomach are considered incurable on clinical evidence alone, and another 35 per cent are designated hopeless at laparotomy, due to other intra-abdominal findings. Of the remainder, ten to twenty per cent undergo palliative surgery such as gastroenterostomy or gastrostomy, while in only fifteen to twenty per cent of cases, a resection is performed with the hope of cure.

This curative operative procedure may be subtotal or total gastrectomy, and may include resection of nodes, spleen, distal half of pancreas, transverse colon, liver edge, duodenum, or lower oesophagus.

The mortality rates for gastrectomy were once so high as to form a formidable contra-indication for surgery. But better pre- and post-operative techniques, and a more complete understanding of gastric function have caused a steady decrease in past years. Current reports indicate a mortality of 0.2 per cent in exploratory operations, of about three per cent for subtotal gastrectomy, an dabout 18 per cent for total gastrectomy.

PROGNOSIS

Patients with known gastric cancer can be expected to die within four to ten months if surgical intervention has not been attempted. The course is progressively downhill. Those cases which receive palliative surgery only do slightly better, and may survive an additional three to five months. Those who have been treated with surgical resection in the hope of cure, have a prognosis of two to four years, although isolated cases have survived much longer.

THE PROBLEM

The problem in our present unsatisfactory management of gastric malignancy is that while surgical treatment

of early gastric carcinoma is relatively good, late cases of the disease can often only be regarded as hopeless. Yet, unfortunately, only these late, incurable cases are generally being diagnosed.

Early diagnosis is then the answer to stomach cancer, and must become the object of mass-education work and mass investigations.

EDUCATION:

1) LAY PEOPLE—must be warned of the insidious onset of this disease and educated to recognize that early symptoms such as fatigue, anorexia, indigestion, fullness after meals, nausea, weakness, etc. should cause them to seek out immediate medical attention.

Let us put up neon lights in every restaurant shrieking at the public: "Indigestion does not start after forty in a man who has been able to eat anything till then" (Boyd).

2) DOCTORS—must be warned to withhold any palliative therapy for a patient in the cancer age group who complains of mild G. I. symptoms as above, until the true cause of the symptoms is established.

Furthermore, doctors must be educated to realize that any change in the normal digestive habit of an older person, male or female, may have an ominous significance.

INVESTIGATIONS:

Routine or mass examinations for gastric carcinoma by X-ray, may be carried out on large groups of people in the cancer age group. This can conveniently be carried out during general physical examinations on:

1) Members of Veterans' clubs
2) Industrial workers
3) Labour unions members
4) Life insurance applicants
5) Patients in hospital.

In addition, any person in the cancer age group with pernicious anemia, or with achlorhydria or hypochlorhydria, or with an unexplained anemia or bleeding, should be thoroughly investigated for carcinoma of the stomach.

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Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing.

VOLTAIRE

CANCER OF THE LUNG

K. J. SOUTHWOOD, 5T2

INCIDENCE

Cancer of the lung occurs next in frequency only to cancer of the gastro intestinal tract, and is responsible for approximately 10 per cent of deaths from cancer. In fact, in recent years, there is evidence indicating that, at least in males, it is the most common visceral cancer. From statistical studies made in hospital centers in New Orleans, St. Louis and Hines, Illinois, it was found that primary cancer of the lung occurred more frequently than did primary cancer of the stomach. That the incidence of lung cancer is increasing has been borne out by many observers. For instance, Kenneway and Kenneway in a careful statistical study of death certificates in England and Wales from 1928-1945 have presented sound evidence of a great increase in deaths due to lung cancer. Also, in America, statistics compiled by the American Cancer Society, show a similar trend during the past two decades. However, it must also be remembered, that improved methods of diagnosis, and a fuller knowledge of the symptomatology, has led to a more frequent recognition of the disease, and also that more people are surviving to reach the cancer age group than was formerly the case. For these reasons it still remains more or less a matter of opinion as to whether the incidence of lung cancer is actually increasing or not.

On an average of all cases of primary lung cancer, 9 per cent develop between the ages of 21 and 40; 80 per cent develop between the ages of 40 and 70. It is predominantly more common in males.

ETIOLOGY

The etiology is as yet unknown. Many theories and possible etiological agents have been suggested, but as yet the evidence for any one factor is inconclusive. Chronic irritation from chemical, mechanical, bacterial, radioactive or perhaps thermal means appears to play an important role in its production. The waste products of automobiles and various petroleum products have been blamed, and certainly the increased usage of such products parallels the apparent increased incidence of lung cancer. For centuries, there has been a very heavy incidence of lung cancer among the workers in the cobalt mines in Schneeberg, Germany, although no cases occurred in persons living in the same district who did not work in the mines. A similar situation is found among the workers in the pitchblende (radium) mines in Bohemia. Here, 90 per cent of all malignant tumors occur in the lung. However as borne out in practically every survey that has been conducted on bronchiogenic carcinoma, the occupational factor itself appears to be of little importance. Patients with the disease come from all sections of every country, from all walks of life and have a great variety of occupations.

This brings us to the consideration of a more common factor, that of tobacco smoking as a possible cause of the lung

cancer. From as early as 1927 this has been a strongly suspected factor. In 1937 Roffe produced experimental cancer in rabbits' ears by the application of tobacco tars. In 1941 Ochsner and De Bakey called attention to the similarity of the curve of increased sales of cigarettes in America to the greater prevalence of primary cancer of the lung in humans. In 1950 Graham and Wynder published a report on 648 cases of proven bronchiogenic carcinoma. As a result of this survey they found:

(1) Of 605 males, 96.5 per cent were moderately heavy to chain smokers for many years, as compared with 73.7 per cent among the general male hospital population without lung cancer.

(2) The occurrence of lung cancer in a male minimal or non-smoker is very rare, about 20 per cent.

(3) 96.1 per cent of patients with the disease, who had a history of smoking had been smoking for at least 20 years. Few women in the cancer age group have smoked for this long, and this fact is believed to be one of the chief reasons for the greater incidence in males to-day. It remains to be seen whether the greater number of women smokers to-day will result in an increased incidence of the disease in females in the next few years.

(4) There may be a lag of 10 years or more between the cessation of smoking and the appearance of clinical symptoms of the disease.

(5) 94.1 per cent of the males were cigarette smokers, 4.0 per cent pipe smokers and 3.5 per cent cigar smokers.

In a survey of 20 hospitals in London, England, between April 1948 and October 1949, Doll and Hill interviewed 709 patients with proven lung cancer. Of this group 649 were males and 60 were females. Of the proven cases, 0.3 per cent of the males and 31.7 per cent of thewomen were non-smokers. Of a non-cancer control group 42 per cent of the men and 53.3 per cent of the women were non-smokers. Of the proven cases again, 26.0 per cent of the men and 14.6 per cent of the women smoked 25 or more cigarettes a day, while in the non-cancer control group only 13.5 per cent of the men and none of the women smoked as many as 25 cigarettes per day.

Arsenic, which is considered a carcinogenic substance was found by Kenneway and Daff in 1950 to be present in cigarettes. This is one of the basic compounds being used in insecticides which have been used with increasing frequency by tobacco growers during the past few years. Whether this factor has anything to do with the production of lung cancer is pure speculation; however, it is a factor to be considered.

With further regard to smoking, Dungal in a report made from studies in Iceland found that of 1,939 autopsies done in Reykjavik from 1932 to 1948, there were 417 malignant growths and only 12 of these were cases of primary lung cancer. He attributes this comparatively low incidence of lung cancer to the fact that smoking, particularly cigarettes, has only recently become popular in Iceland. It remains to be seen whether the incidence of primary

lung cancer increases in Iceland during the next 20 years.

PATHOLOGY

Primary cancer of the lung arises in the majority of cases from the bronchial epithelium, and in a few cases from the bronchial mucus glands. The right lung is more often involved than the left, and the upper lobes more often than the lower lobes. 75-80 per cent arise at or near the hilum, usually in the primary division of a main bronchus; 20-25 per cent arise in the lung periphery.

Grossly, the most common finding is a firm grayish-white tumor in the hilar region either as a papillary projection into the lumen of a main bronchus, or merely as a roughening of the mucous membrane of the bronchial wall with some narrowing of the lumen. The tumors arising from the smaller bronchi in the lung periphery tend to be more circumscribed, which makes surgical removal easier.

Microscopically, cancer of the lung can be divided into three histological types:

(1) The highly undifferentiated or anaplastic type, in which the cells may be small and round, spindle-shaped, or oval, the oat cell type carcinoma. This group tends to occur at an earlier age, and spreads widely and rapidly.

(2) The more differentiated glandular or adenocarcinomatous type in which the cells are cubical or columnar and may be collected in groups (medullary arrangement) or arranged around gland-like spaces into which papillary processes may project (adenocarcinomatous arrangement).

(3) The most differentiated, squamous cell or epidermoid carcinoma. This group presents the most favourable prognosis for the patient due to the fact that it spreads very slowly, remaining localized for quite some time. Lymph node involvement is not marked, and blood stream metastases are rare.

Spread may be through the lung substance via the peribronchial and perivascular lymphatics, to the lymph nodes, first to the regional nodes, i.e. the tracheo-bronchial and mediastinal nodes, and from these to more distant lymph glands: supraclavicular, axillary, cervical, etc. Blood stream metastases to distant organs are very common, the order of frequency being liver, brain, bone, kidney and adrenal, and less commonly to the pancreas, thyroid and other structures. Similarly secondary cancer of the lung is very common via lymphatic and blood stream metastases. The commonest secondaries are sarcoma, malignant melanoma, chorionepithelioma, and hypernephroma.

SYMPTOMS

The main symptoms of the disease are cough, hemoptysis, wheezing, shortness of breath, symptoms of lung inflammation, pain, constitutional symptoms, and symptoms of metastases.

Cough is present in about 90 per cent of the cases, not always as an early symptom however. The characteristic cough is of the hacking type which may or may not be accompanied by sputum. Any change in cough habits should be

regarded with suspicion. For instance, the development of a smoker's cough in a person who has previously smoked heavily without a cough, or a sudden increase in severity in a chronic cough that has been present for many years, and has become to be regarded as a cough habit, or a cough which develops during a respiratory illness, and persists following the clearing up of the illness, should all be watched carefully.

Blood spitting is an important symptom in about 50 per cent of cases. It is rarely an initial symptom, for the history will usually reveal the presence of earlier chest symptoms. A sudden large hemoptysis is uncommon in early cases. The most common form of blood spiting in the early stages is streaking of the sputum with blood; it is rarely mixed with the sputum, and persistent daily streaking of this nature is almost pathognomonic of cancer of the lung. It may however, only occur once or twice during the whole course of the disease.

Wheezing is a symptom which is often overlooked because it is transient or because it causes no particular distress. This symptom occurs in approximately 40 per cent of cases.

Shortness of breath is usually moderate or slight and occurs in approximately 60 per cent of cases. It has an incidious development beginning as breathlessness or unusual exertion, which is usually attributed by patients to being "out of condition," or "getting on in years." The patient then remedies this situation by reducing his activity and forgets all about it until it either increases to a true dyspnoea, or other symptoms make their appearance.

In cancer of the lung, all the factors required for *inflammation* are present. There is mechanical obstruction, retention of secretions, and pathogenic bacteria are present. The nature of the inflammation ranges from mild influenza to lung abscess or empyema depending upon the type of organism present, the resistance of the host and the degree of obstruction.

Pain is a symptom in about 50 per cent of cases, and unfortunately, due to nerve involvement is a major symptom in the later stages. The pain may be pleuritic, deep-seated, or may be referred to the shoulder, arm, epigastrium.

Constitutional symptoms are usually minor in character and variable in constancy, but they may be severe, particularly in the peripheral type of growth. They include lassitude, depression, listlessness, lack of energy, a "washed out" or run-down feeling. Characteristically the patient may feel well on some days and quite ill on other days. Such symptoms are, however, often present among apparently healthy members of the community and most patients carry on as long as they can do their daily work. But, if a patient should appear with these minor complaints along with associated chest symptoms, one should be suspicious of lung cancer.

Symptoms resulting from metastatic growths rather than the primary lesion in the lung may be responsible for the clinical symptoms. This is particularly true of mediastinal metastases resulting in superior vena caval obstruction, hoarseness, cardiac arrhythmia, and dysphagia. A disposition change may suggest a brain metastasis.

A tumor in the lung apex presents a collection of symptoms known as Pancoast's-syndrome which is characterized

by local destruction or erosion of the first two or three ribs, paralysis of the sympathetic trunk producing a Horner's syndrome, pain about the shoulder and down the arm with partial paralysis of the ulnar and median nerves and subsequent atrophy of the muscles of the hand. Most of these cases are examples of apical bronchiogenic carcinoma pressing on the brachial plexus and the sympathetic cervical chain, but without signs of pulmonary disease.

DIAGNOSIS

At the present time about 50 per cent of all cases of cancer of the lung are diagnosed clinically, though unfortunately, in the majority of cases, the lesion is too far advanced for efficient treatment. X-rays make the diagnosis in about 23 per cent of these cases, using both antero-posterior and lateral views; bronchoscopic biopsy yields a positive diagnosis in 60 to 80 per cent. Cytological studies of bronchoscopically aspirated secretions and sputum are probably the greatest aids in arriving at an early diagnosis. McBurney and Patton in studies conducted at the Mayo clinic report a diagnostic accuracy of 80 to 90 per cent by cytological examination. It must be remembered however, that only in the hands of an expert bronchologist and a specially trained examiner can such a high percentage be attained. Exploratory thoracotomy is justified when the above methods give a negative result, but the clinical findings are strongly suggestive of lung cancer.

PROGNOSIS

The prognosis remains very grave, mainly due to a delay in diagnosis. Kulvin in a series of 266 cases of bronchiogenic carcinoma found that only 13 were still alive 12 months after the diagnosis had been made.

TREATMENT

In studies made at the Mayo clinic on all proven cases of lung cancer from 1906 through 1948, McBurney reports, of 90 cases of small cell carcinoma, 29 had exploratory thoracotomy, and 15 of the 29 had a pneumonectomy. All the latter were traced; 2 were still alive, one 5 years and 4 months, the other 2 years and 9 months after operation. All but 6 of those who did not have exploratory thoracotomy or whose lesion could not be removed surgically were traced, and all were dead. The six untraced cases had hopeless malignancy to start with. Patton, in the same survey, found in all cases of the squamous cell type that the 2 year survival rate with resection was 3.6 per cent and that no patient lived 3 years without lung resection.

The results of a survey on 210 patients with lung cancer by Shaw in the past 3 years show that 50 per cent were inoperable when first seen because of metastases, severe cachexia or invasion and spread within the chest to such an extent as to make total removal impossible. Of the remaining 50 per cent is was subsequently found on exploratory thoracotomy that 50 per cent of this group were inoperable. This meant that only 25 per cent of the original 210 patients were suitable for pneumonectomy. In a portion of this 25 per cent only palliative treatment was being attempted, since there was no chance of a complete cure. In the 70 resections carried out there was 5 deaths, an operative mortality of 6 per cent.

In view of the age group of the patients and the technical difficulties involved in pneumonectomy, it is not likely that the operative mortality rate can be appreciably reduced. Therefore, the only hope of improving the overall results in the surgical treatment lies in its early detection. A review of the history of these patients showed there was a delay of 5 months, approximately, between the time the patient first experienced symptoms and his first visit to a doctor. This delay is difficult to eliminate. Of more significance however, was the delay between the time the patient presented himself and the establishment of a correct diagnosis. In this group, an average of 6 months elapsed. This delay can possibly be remedied. It has been estimated that for each month's delay between the time of diagnosis, when the patient is in an apparently operable state and the actual time of operation, that the patient loses about 15 per cent of his chance of obtaining eventual cure. The delay in most instances is due to an original error in diagnosis, such as: unresolved pneumonia, virus pneumonia, tuberculosis, asthma or bronchitis.

The average survival time of patients with untreated lung cancer, after the diagnosis has been made is 9 months; but not infrequently a patient may live for 2 years or more. With successful removal of the primary tumor, the patient can be expected to live longer, though 5 and 10 year survivals are still few. On an average, of those operated on, 25 per cent are well in 3 years and 22 per cent are well in 5 years. That is to say, of every 100 cases of diagnosed lung cancer, only 5 will be alive in 5 years time.

The treatment of inoperable cancer is only palliative in nature in an endeavour to make the patient as comfortable as possible. X-ray therapy or nitrogen mustard (mechlorethamine) given intravenously in an average dose of 0.1 mg./kg. of body weight per day for four days may give transient general improvement and alleviation of distressing symptoms in some patients for from 2 weeks to 2 months. However, treatment of subsequent relapses is usually not as successful as the first course and succeeding treatments tend to have a steadily decreasing effect on the disease. These patients also will require progressively increasing amounts of narcotics and sedatives, because unfortunately in the later stages, due to extensive nerve involvement, pain is a major symptom of lung cancer. Patients with bronchial or tracheal obstruction may also require oxygen, bronchodilators, or even helium and oxygen terminally.

SUMMARY

This has been a brief review of cancer of the lung in which certain aspects, notably the possible etiological significance of smoking, and the statistical results of treatment, have been stressed. Emphasis has also been laid on the pathology and symptomatology of this condition in the hope that diagnosis may be facilitated, and the rate of cure increased thereby.

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ANSWERS TO "SIGNS AND SYNDROMES" QUIZ (PAGE 152)

1. VII nerve irritability seen in *tetany.*
2. Pressure under right subcostal margin giving pain in *acute cholecystitis.*
3. Blue discolouration of umbilicus in *ectopic pregnancy.*
4. Painful leg raising giving *meningeal irritation.*
5. X-ray showing halo (meniscus sign) around *malignant gastric ulcer.*
6. Pain at McBurney's point in *acute appendicitis* induced by pressure over descending colon.
7. Diagnostic sign in *pregnancy.*
8. "Lid-lag" in *hyperthyroidism.*
9. Dilated gall bladder in *carcinoma of head of pancreas.*
10. Murmur heard over x femoral artery in *aortic regurgitation.*
11. Notch in medial border of tibia (seen in X-ray) in *congenital syphilis.*
12. Failure of C.S.F. pressure to be elevated on compression of jugular veins due to *blockage in subarachnoid space.*
13. ECG sign in *myocardial infarction.*
14. Flexion of legs with passive bending of neck seen in *meningitis.*
15. Carpo-pedal spasm produced by brachial artery compression in *tetany.*
16. Hyperesthesia over the back in *acute cholecystitis.*
17. Bluish discolouration of vaginal mucosa in *pregnancy.*
18. Sagging of pelvis when patient stands on affected leg in *congenital dislocation* of hip.
19. Widening of palpebral fissure in *hyperthyroidism.*
20. Swaying stance with eyes closed seen in *Tabes dorsalis.*

THE UNIVERSITY OF TORONTO
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EDITORIAL

A GREATER TORONTO GENERAL HOSPITAL

We are told (and not too infrequently) that the Doctor is a person of some importance in the Community and as such he ought to engage himself in community affairs. We at Toronto are fortunate in having a complete medical curriculum which includes, of course, many opportunities for learning to take part in community projects. All this naturally fits into the current campaign for funds to extend and modernize facilities at the Toronto General Hospital, and it is fitting therefore that students be asked to contribute to this programme.

That a warm, personal and unique relationship exists between the student of Medicine and the teaching hospital can not be denied. At Toronto, we are singularly fortunate in having access to numerous and distinguished teaching centres, not the least of which is the Toronto General Hospital. It is in his three senior years that the student is intimately connected with this centre and it is here that he learns the arts and sciences of his profession.

To answer the question of whether the undergraduate will benefit from this campaign one has only to contrast the expansive teaching facilities at the new Toronto Hospital for Sick Children with the present overcrowding at the "General" and to realize that the best in clinical teaching occurs only when the teacher, no matter how renowned he may be, meets his students amidst

spacious and well-equipped surroundings.

But the student is apt to consider himself as a breed of man distinct from most—accepting privileges from all but owing responsibility and allegiance to none. Too often, in campaigns of this nature, one meets with the lethargic response, the passive attitude and the indifferent approach. It is well to realize that such indifference will lead eventually to the bogey-man of bureaucracy and to the autocrat of officialdom. Surely, in this age of modern advertising, when we are accosted at every corner with claims for superiority in merchandise, movies and motor cars, we will rarely be presented with such a worth-while opportunity for investing in our own future.

For those of the graduating year who will not benefit directly from this campaign—let your contribution be a token of affection and appreciation; but for those who have yet to come, look upon it as a shrewd investment that will bear you much interest in the years ahead.

We feel confident that the medical student will join with the citizens of Ontario and Toronto and with the members of the teaching staff in contributing to this campaign for a "Greater Toronto General Hospital."

A. M. R.

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PERSONALITIES IN WESTERN CANADIAN MEDICINE*

N. D. ABBEY, 5T3

This paper will be concerned with a group of men who might be called "Our Neglected Heroes." These are the men who pioneered medical services in that part of Canada bounded on the west by the Rocky Mountains, on the east by Hudson Bay, on the south by the International Boundary, and in the north by the great ice fields of the Arctic.

In this vast territory the first permanent general practitioner was William Morrison McKay. Dr. McKay studied in Edinburgh under such great teachers as Simpson, Lister and Syme. In 1864 he became surgeon to the Company of Gentleman Adventurers trading into Hudson Bay. As a scene for future exploits McKay chose the McKenzie River Basin. Here he devoted thirty-four years of his life to a very active medical practice.

An interesting story is told of an incident that happened at Fort Simpson in 1868.

"Mrs. McKay tells of one occasion when one of the Company's employees was gored by a bull and suffered from a large gash in the abdominal muscles. The doctor selected the instruments and prepared to sew up the wound. When all was ready he turned to his wife and said, 'You're better at this work than I am, you sew this up.' Accustomed to the making of moccasins and the deerskin costumes of the country, Mrs. McKay put twelve stitches in the belly wound and was quite proud of the fact that the patient made a speedy and permanent recovery."

For her services at this time we might call Mrs. McKay the first practising woman physician in the West.

Drugs used by McKay were few and inefficient. Epsom salts, rhubarb and grey powder served for many a patient whose complaints called for a more effective but absent remedy.

Although McKay was the first permanent practitioner in the West, there were many before him who were mainly explorers or botanists who came to this new undiscovered land in search of adventure. These men included Dr. John Richardson, who passed through Fort Edmonton with the Franklin Polar Expedition in 1820. In 1834 Richardson and Dr. John Rae from Winnipeg returned to this area in search of the remains of the Franklin Expedition. Sir James Hector, a well known botanist and biologist, visited the West in 1857 with the Palliser expedition. It was Hector who named Kicking Horse Pass in the Rocky Mountains, having had the unfortunate experience of being kicked by a horse at that time. In 1865 Dr. Cheadle came out with the Lord Milton expedition. His remarks on the American tongue are worth noting—"to talk Yankee, accent every word the opposite of English, and with 'I guess,' 'now' and 'kinder' and a nasal twang you are complete." These latter two men have mountain peaks in the Rockies named after them.

In the period between 1870 and 1890 medical practice was often combined with the activities of the Royal North West Mounted Police (R.N.W.M.P.),

*An address to the Osler Club.

the Riel Rebellion and the Canadian Pacific Railway. The description by Captain Butler of the R.N.W.M.P. of an epidemic of smallpox that took place in our country not more than seventy years ago is well worth mentioning.

"It is difficult to imagine a state of pestilence more terrible than that which kept pace with the moving parties of Crees during the summer months of 1870. By streams and lakes, in willow copses, and upon bare hillsides, often shelterless from the fierce rays of the summer sun and exposed to the rains and dews of the night, the poor, plague stricken wretches lay down to die—no assistance of any kind—for the ties of family were quickly loosened and mothers abandoned their helpless children upon the wayside, fleeing onward to some fancied place of safety."

The medical men chiefly concerned with the R.N.W.M.P. and the Riel Rebellion were Sir Thomas Roddick, Dr. A. L. Jukes, and Dr. Barrington Nevitt. Roddick was the first Surgeon General for Canada and was made responsible for setting up Canada's first Army Medical Corps during the Riel Rebellion. When the call went out for volunteers the entire body of medical students in the Dominion volunteered their services.

At the close of the Riel Rebellion in 1885 Louis Riel came under the medical care of Dr. A. L. Jukes in the Ward room at the N.W.M.P. barracks in Regina. It was Jukes who published the "Sanity Report" over which there was so much controversy in Canada at the time. One of Riel's remarks to Jukes is worth while.

"Sir, a man may be able in taking care of the sick, he may understand his cases very well, and his medicines well chosen, but above all that, the blessing of God is needed and without it there is no true success."

Dr. Nevitt ('74 Toronto) was associated with the N.W.M.P. for a short time before he returned to the East in 1882 to become professor of sanitary science in the Women's Medical College. Later in 1889 he became Dean of the College. Dr. Nevitt was referred to by the male medical students as Mrs. Nevitt. During the excursions through the wards of the old T.G.H., Dr. Nevitt was always attached to a flock of "lady meds" who, according to the theory of that day, were too coy and unsophisticated to be unduly exposed to the molestation of the "dirty meds" but most of whom, in the fact and candor of this later day, would have been considered absolutely safe, even in the dark.

The name of Dr. R. G. Brett is linked with the building of the Canadian Pacific Railway. Dr. Brett, who came to Banff in 1883, was a prominent medical and political figure in this area until his death in 1925. At Banff Dr. Brett was associated with many types of people.

"Guileless tourists and guileful guides, excited mountain climbers and restful broncho ponies, versatile souvenir exploiters and trustful victims, swimmers and fishers and hunters and skiers; Arthritics and rheumatics, neurotics and psychotics, alcoholics and dyspeptics; people who were really sick although too poor to be so, people who only thought they were sick but too rich to be healthy."

Brett's familiarity with people is expressed by an incident which happened when Brett as Lieutenant-Governor was scheduled to visit a small settlement. When the special train arrived at the

small station crowded with people, the dignified representative of the King stepped out on to the platform. An old miner who had pushed his way up to the front to get a look at the dignitary, took one look at him and then turned to the crowd and shouted, "Hell, it's only old Doc Brett!"

A great heritage has been built up in the West around that nebulous figure —the general practitioner. Imagine yourself to be a young adventurous graduate of Toronto in the year 1900. What did the West have to offer? Wealth? Hardship? Rewards? Adventure? Yes, it had all of these and more!

Your office might not be of the highest quality. "Dr. E. M. Sharpe of Lacombe, Alta., decided without prejudice to locate as a young bachelor and practicing physician in the only available room in the community, making it serve the double purpose of living quarters and professional consulting office. The room was upstairs over the harness shop and was part of the harness-maker's private home. Its furniture included a sofa, dresser, a couple of chairs and a double bed. The contract for the bed carried with it a joint partnership stipulation for the four year old son of the family whereby the doctor was assured of his sleep when the child became too weary to keep him kicked into wakefulness."

Transportation would always be a problem. The horse and buggy served the purpose in the summer and in the winter a cutter, buffalo robes and a long hard journey in cold weather were the lot of the doctor. The story is told of Dr. L. G. DeVeber* who rode 167 miles on horseback in 18 hours. The journey required four horses, one of which was reported to have been unbroken when the doctor started, but certainly well broken when the journey was over.

Some of the more amusing incidents in obstetrical practice in these early times were the following.

Dr. Rouleaux a well known and well loved French-Canadian practitioner, whose advice to expectant mothers was, "Courage, Madam, Courage," has this story told about him.

"Often, of course, a new mother would complain of the sex of the newborn. The doctor would advise, 'Madam! take what de good God sends you and thank God it is all right.' But one mother who was presented with another son, already having five, was in hysterical rebellion. The doctor only managed to temporize her by saying 'Perhaps then I can put him back and de good God may make him into a girl!' "

Another doctor tells us this story. "About 1905 I was attending a maternity case in a home. The husband was absent at some mining camp. Nembutal had not yet come into vogue and Dr. Chipman's rule, 'Lady! you have to dilate your own cervix,' was considered the correct procedure. Pains were described as smart when they were really severe. It was my practice to give chloroform when delivery was approaching. My guess was that this woman thought I was about as good as nothing. As I sat dreaming about a late dinner, she blurted out after a strong pain, 'I wish my old man was here!' Innocently I remarked, 'I don't think he could help you.' 'Help me!' she screamed, 'Help me, I want to wring his neck!' "

Hospitals were few and nursing

*Grandfather of Barry and George DeVeber of Meds 5T3 and 5T6, respectively.

mostly on a practical level. Operations were performed under unusual circumstances. Frank Hamilton Mewburne of Lethbridge was a forceful, aggressive, self reliant, square shooting, colorful and perhaps profane surgeon. "During one operation on a priest, Bishop Legal was asked to give chloroform while Memburne and Dr. Kennedy operated. A fly persisted in buzzing its song into his ear. Kennedy strove in vain to keep his confrere's impulsiveness submerged. But it was too much to expect. 'Kennedy,' blurted out Mewburne, 'Kill that fly or put the Bishop out. I don't give a damn which, I can't hold myself any longer.' "

On another occasion Dr. Mewburn was worsted by a woman. Miss McDonald, the first nurse belonging to the Victoria Order of Nursing in Alberta, received a call to assist Dr. Mewburn in an operation at Lundbreck. Forewarned of his reputation she was ready for him. The patient was laid out on the dining-room table. As the operation proceeded Miss McDonald was holding a lamp with one hand and an ejector with the other. The case was a desperate one. Orders came thick and fast from the surgeon. 'Hold the lamp here! no—there! and, hold it high, d—— it, hold it higher!' 'Hold it yourself, damnit, I've only got two hands,' retorted the exasperated nurse. Later, Dr. Mewburn introduced her as the only woman who could swear better than he could."

Fees were collected in unusual ways and sometimes involved an ethical problem. "A man named H——— and his wife didn't get along very well together, and that puts it mildly too. She always referred to him as 'that old brute H———' and he wasn't any more complimentary in his remarks regarding her. However, she handled the money. One afternoon she became quite ill. H——— looked me up and said, 'The wife is sick. I want you to go up and see her. If she gets better, she'll pay you, if she doesn't, I'll pay you and pay you damned well!' "

This story is told about Dr. Neville James Lindsay, Calgary's first resident physician.

"He had left many things behind him but not the 'two-bit' psychology of the Ontario profession of those days regarding medical fees. It still permeated his medical soul. His first patient was a cowpuncher with a colles fracture. Lindsay had not familiarized himself with the western schedule, but to make certain his fee would be high enough he decided to double the usual Ontario fee of one dollar. The cowboy looked at the doctor in disdain, threw him a ten-spot and blurted out, 'Hell, Doc! you'll starve around here if you don't do better'n that. Here's ten bones anyway and I'm forty ahead of you at that!' Lindsay learned his lesson with his first case."

It is interesting to note that Dr. Lindsay retired at the age of sixty-five to look after his vast financial enterprises.

These men that have been described were not discoverers of new drugs or new treatments; their discoveries were ones which involved the intimate workings of minds and hearts of their patients. They were the artists, rather than the scientists of Medicine. This is our heritage.

ACKNOWLEDGMENTS

I would like to thank Dr. E. P. Scarlett of the Calgary Associate Clinic and Miss Poole of the Academy of Medicine for their help in preparing this paper.

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SUMMER INTERNESHIP IN THE UNITED STATES

D. G. WATSON, 5T2

INTRODUCTION

This article is based partly on a summer interneship at the Milwaukee Hospital, Milwaukee, Wisconsin, and partly on talks with several classmates who had similar experience mainly in the North-Eastern United States. Such an interneship offers unique opportunities, and also some problems.

POSITIONS AVAILABLE

The positions available were short-term rotating interneships with the same duties and responsibilities as "regular" interneships. Some hospitals have openings for technicians in their clinical, laboratory or pathological departments. The remuneration varies—$50–$100, or more per month, plus a room in the interne's quarters, board and laundry. Most offer a teaching program with lectures, discussions, and clinical pathological conferences.

ADVANTAGES AND DISADVANTAGES

Many students in the summer preceding their senior year wish work which will give them medical experience: in the medical branches of the Services, in special government services, with practitioners, or in various types of hospitals. There are several very distinct *advantages* to summer interneship in the United States.

(1) Few well-qualified medium-sized Canadian general hospitals offer full interneship training to summer students, whereas numerous U.S. hospitals with high medical standards and well-rounded training programs will. Such training gives a student a valuable background for his senior year and helps prepare him for graduate interneship.

(2) It is enlightening to be away from one's home teaching centre and to view it from a different perspective. While Toronto may not be as medically dominant as some would have us believe, it appears to rank gratifyingly high amongst North American medical centres.

(3) Many American hospitals are wholly private. This provides an interesting contrast to public ward patients and helps better to train one for private practice.

(4) The fact that one is away from home, living with Americans in the United States, helps broaden his education and make the summer less like work and more like a vacation.

(5) From personal experience, U.S. hospitals appear more prompt, courteous and explicit in their correspondence, usually replying to letters by return air mail.

There are also *disadvantages*:

(1) The distance from home with associated transportation and other personal problems.

(2) Decreased opportunity to investigate fully the chosen hospital.

(3) The concentration on practical work and the long hours which make relaxation and medical reading difficult, in the last summer in which a student has much chance for either.

SELECTION OF HOSPITAL

The selection of a hospital is very important. There is a marked interne shortage in the United States. Thus by corresponding with several hospitals one should have little difficulty locating one or more suitable interested hospitals with full qualifications. I suggest that any interested student should choose the hospitals on the recommendation of medical friends in the United States, of Canadians who have interned there, or by perusing the list of hospital prospectuses in the T. G. H. students common room. While these latter hospitals are primarily interested in graduate internes many have openings for summer internes also. Finally, one should refer to the American Medical Association Directory in the Medical Reading Room, both for a list of hospitals in any desired centre and also to check the qualifications of any one particular hospital. Preferably, the hospital should be approved by the A.M.A. as a first-class general hospital, and approved for both interneships and residences; it also should be approved by the American Board of Surgeons. The directory also lists the number of beds and the name of the administrator or superintendent.

IMMIGRATION REGULATIONS

A Canadian employed in the United States requires a visa. For such purposes the U.S. has devised the Visitor's Exchange Visa. Once accepted by a hospital, one should request the hospital to apply to the State Department, Washington, D.C. for listing with the Visitor's Exchange Program (provided they are not already listed). The hospital will be assigned a number (e.g. P-547). One next makes an appointment at the U.S. Consulate, 360 University Avenue, and takes with him his letter from the hospital (stating that they wish his services for the summer and confirming their program listing number) plus two passport photos and a Canadian passport. It takes about five dollars and four weeks to obtain a passport and application forms; instructions are available at all post offices. Also advisable, but not essential, is a letter from the local police chief stating that the student has no criminal record. Due to the above formalities one should commence correspondence in February or early March. He should also visit the U.S. Immigration Office, 360 University Avenue, to make sure these regulations have not changed.

SUMMARY

Third year students who are planning their summer employment would be well advised to consider interneship in a first class medium-sized American hospital. The work is hard but there is a wealth of diagnostic and therapeutic clinical experience available; those who availed themselves of it this last summer were all enthusiastic.

While stating that the United States offers advantages to the summer interne, this article is in no way intended to promote *graduate* interneship outside Canada. Though completely satisfied with his medical experience in Milwaukee and grateful to the excellent clinicians there who were very kind and helpful, this student plans to interne in Canada.

ABSTRACTS

SURGERY

Diabetic Gangrene: Greenberg, A., et al. B.M.J. 1254-57 (Nov. 24) 1951.

Evidence is presented which contraindicates the radical amputations which are still often employed in the treatment of diabetic gangrene. Diabetic gangrene is divided into two types: (1) where infection is the primary factor (especially in younger patients); and (2) where occlusive vascular disease is the exciting cause (especially in senile patients).

The details of 50 cases are reported with follow-ups ranging from 2 months to 6 years. The routine treatment was outlined as follows:

(1) Control of infection. The organisms were identified and their sensitivity determined, if possible, so that the correct anti-bacterial agent could be used. Systemic penicillin or streptomycin as indicated were usually employed.

(2) Control of diabetes. The younger patient with primary infective gangrene was much more difficult to control than the elderly patient.

(3) X-ray plate of foot. To exclude bone necrosis due to osteomyelitis or suppurative arthritis. Bone necrosis was used as a guide to the extent of surgical excision.

(4) Surgery. Only local surgical excision of necrotic tissue was performed. The part was inspected for deep sepsis and infected tracks laid open. Bleeding from the margins of the wound was considered a good prognostic sign. These workers got better results by amputation through the proximal phalanx rather than disarticulation at the metatarso-phalangeal joint as the disarticulation had a tendency to impair the blood supply to the adjacent toe and had led other surgeons to recommend amputation of all the toes as a preventive measure.

Of the 50 cases studied 29 were primarily infective in type, 16 primarily vascular and 5 a combination of the two types. The results of the conservative surgery appear to have been very satisfactory and most of the patients are ambulatory. These results contrast sharply with those obtained in non-diabetic senile gangrene, which almost inevitably necessitates above-knee amputation. Indeed the authors find that gangrene in non-diabetic patients is far less amenable to conservative surgery than in diabetics of the same age.

The theory is advanced that the diabetic tendency to early, slow, progressive, atheromatous occlusion of the vascular lumen stimulates the formation of a collateral circulation, which is usually well established when the crisis of peripheral vascular thrombosis supervenes.

S. Libracii

Cardiac Arrest During Surgery: Corff M., Amer. J. of Surgery, 82: 6, Dec. 1951.

Cardiac arrest is an uncommon surgical emergency which when present requires immediate treatment. The arrest may occur during any type of operation on any part of the body and with any anesthetic agent. It is more common with operations on the heart, especially the diseased heart, and on carotid body tumours. After 3 to 5 minutes of anoxia irreversible cerebral changes occur. When resuscitation saves life but does not prevent brain damage, the results may be some permanent neurological changes.

The cause is not well known. The author attaches importance to the following causes: 1. Excessive deep anesthesia; 2. Hypoxia; 3. Stimulation of the vagus nerve; 4. Manipulation of the carotid sinus; 5. Drug sensitivity; 6. Surgery with too light anesthesia.

Cardiac arrest is diagnosed by absence of pulse and blood pressure. The author states that arrest is of two types—ventri-

cular standstill and ventricular fibrillation.

Treatment consists of: 1. 100% oxygen therapy; 2. Cardiac massage at a rate of 60 per minute; 3. Epinephrine, Procaine and Atropine; 4. Electric shock therapy directly to the heart if fibrillation is present; 5. Intravenous blood plasma or saline under pressure to increase blood flow. This type of therapy usually starts normal spontaneous rhythm of the heart.

The author cites a dramatic case of cardiac arrest where resuscitation was accomplished in one minute.

Although cardiac arrest is uncommon, delay in treatment may be fatal, and surgeons must always be alert for it. The anesthetist and surgeon must work as a team.

M. Wasylenki

PEDIATRICS

Childhood Factors in Duodenal Ulcer: Kellock, T. D., B.M.J., **4740:** 1117 (Nov. 10) 1951.

Duodenal ulcer is characterized by many as a "psychosomatic illness" and there have been attempts in the past to define an adult personality for this type of disease. This has resulted in disagreement among authors.

The importance of childhood in the genesis of adult personality is well recognized; with this in mind, previous writers have suggested many etiological factors such as unstable home life, rejection in childhood, masculine-feminine complexes, early insecurity, and preponderance of brothers or sisters.

The author in 1950 interviewed 500 patients, 250 with x-ray evidence of duodenal ulcer and 250 with various other diseases excluding gastric ulcer. With these patients he carefully tabulated from histories family factors such as sex, number and sex of siblings, position in the family, parental factors such as death, divorce, separation, and age leaving home, age of mother at birth, level of education, childhood illness and social class.

In the analysis of the charts it is clearly seen that no difference in any of the above factors exists between the duodenal ulcer patients and the control group. From this series (the largest so far published) the author concludes that perhaps these factors may not be applicable and that other factors operating in adolescence may be causative, but unless further investigation shows clear-cut differences between duodenal ulcer patients and the general population, the possibility that the "ulcer personality" may be the effect rather than the cause must be considered.

R. F. Lane

MEDICINE

An Explanation of the "Primary Atypical Pneumonia" Syndrome. Robertson P. W. and Morle K.D.F. B.M.J. 994-998. (Oct. 25) 1951.

The authors describe a series of more than 500 cases of what they call an aspiration pneumonia in a group of young men undergoing their first weeks of initial basic military training. This is compared clinically, radiologically and bacteriologically with various series of the primary atypical pneumonia syndrome reported in the literature. The findings in their group were identical with those of reported cases. The illnesses occurred under similar circumstances and followed similar clinical courses.

In discussing etiology they point out that the view of virus causation has arisen largely because no specific etiological factor has been found. They believe that the condition is entirely due to aspiration of products from pre-existing upper respiratory infection, and in support of this view they offer the following as evidence: (1) The condition follows upper respiratory infection, usually nasopharyngitis, but occasionally tonsillitis, sinusitis, tracheobronchitis, or true influenza. (2) All lesions occurred in dependent bronchopulmonary segments or sub-segments. (3) Symptoms often arose after severe physical exercise in which more active respiration facilitated aspiration.

Finally the authors discuss the methods

of treatment. Antibiotics are effective only where specifically sensitive micro-organisms are aspirated. Generally such simple methods as percussion, postural drainage and steam inhalations are often very effective where the aspirated material is non-infected mucus rather than grossly infected mucopus.

T. R. H. Box

Systolic Murmurs in Young Adults: Stewart, I. Br. Heart Jour., **13**: 4, Oct., '51.

The author examined 525 apparently normal young people who were university students and nurses. 365 were men; 160 were women. Systolic murmurs were found in 179 of the 525. Rheumatic heart disease was diagnosed in one subject and suspected in 5 others. From this examination the author concludes and emphasizes the following facts:

1. Innocent murmurs are usually short, appear late in systole, and may be loud but are never rough or harsh.

2. Variability in loudness is the fundamental characteristic of nearly all systolic murmurs heard in young adults. An increased heart rate as a result of exercise or excitement is the most potent factor in augmenting loudness. However, violent exercise will very often produce transient moderately loud murmurs where normally none existed.

3. Higher grades of loudness of apical systolic murmurs very often indicates mitral disease but faintness or even absence of a murmur does not exclude an organic lesion.

4. In only three subjects were persistence and localization in a systolic murmur found together. Two of these had strong rheumatic fever histories. The writer considers the combination of these two factors the most practical criteria for a suspicion of organic mitral or aortic valvular disease.

5. In many young adults, especially robust active ones, systolic murmurs commonly come and go over periods of a few months.

6. The loudest and most persistent murmurs in this series occurred in the ratio of three women to one man. Therefore, there should be increased suspicion of organic disease when such murmurs are heard in men.

J. B. Kopstein

Evolution of the Toxic Thyroid Gland: Levitt T., Lancet, **261**: 6691, Nov., 1951.

After a study on 2114 consecutive patients undergoing thyroidectomy at New End Hospital, Hampstead, the writer concludes that there is a close relationship between the toxic diseases of the thyroid gland. On the basis of 706 thyroids characterized microscopically by epithelial hyperplasia, and 704 thyroids characterized by the presence of varying amounts of lymphoid tissue, he deseribes six phases, each with a different degree of toxicity. Beginning with the epithelial hyperplasia of Graves' disease, there is a transition to increasing amounts of lymphoid hyperplasia which in turn is replaced by fibrosis. Toxicity decreases as the disease progresses.

The six phases are: 1. Epithelial Hyperplasia—Graves' disease; 2. Lymphoepithelial hyperplasia; 3. Focal lymphoid hyperplasia; 4. Diffuse lymphoid hyperplasia; 5. Fibrolymphoid hyperplasia—Hashimoto's disease; 6. Fibrosis—Riedel's disease.

The microscopic and macroscopic features of each phase are discussed and the elinical features of age, toxicity, exophthalmos, lid-retraction, pre- and postoperative change of weight, postoperative hypothyroidism, and recurrence are related to the pathology.

T. Belch

The Use of Vitamin B_{12} in the Management of the Neurological Manifestations of Diabetes Mellitus. Sancetta, S. M. et al. Annals of Int. Med., **35**, 1028, Nov. 1951.

The authors report a series of 12 cases of diabetes mellitus with definite neurolo-

gical manifestations treated with vitamin B_{12}. The possible etiology of these disturbances is briefly discussed and a classification is suggested.

All patients considered showed initially one or more of: absent or depressed plantar response, hypesthesias or paresthesias of the extremities, and ataxia; in addition to other disturbances. No purely subjective disorders were included. Periods of observation varied from one to 13 months.

A satisfactory regimen controlling the diabetes was found necessary before improvement on B_{12} therapy was obtained, but such a regimen alone did not guarantee the non-appearance of neurological symptoms. A flexible dosage routine was used. It is emphasised that massive doses produced no cumulative effect.

This therapy produced definite improvement of most symptoms when present. Paresthesias and hypesthesias showed improvement (with one relapse) greater in upper than lower extremities. Temperature discrimination returned to normal and ataxia disappeared. Leg cramps improved. Constipation was uniformly relieved although "autonomic dysfunctions" such as gastro-intestinal atony and pupillary fixation were unaffected. No improvement in peripheral circulation was detectable and no non-neurological manifestations were affected.

The response of the patients was variable but there was no relation between symptomatology, achlorhydria, or the past or present course of the disease on this response.

The authors conclude that improvement on vitamin B_{12} therapy is neither a psychic nor a vascular effect, but is due to a direct action on intrinsic nerve metabolism. The exact mode of action is unknown.

C. W. Milburn

Diagnosis of Dissecting Aneurysm of the Aorta: Domzalski, C. A., A.M.A. Arch. of Int. Med., **88**: 770-82, Dec. 1951.

This subject is presented with a view to emphasizing (1) the difficulty of correct diagnosis; (2) the importance of differentiation from acute myocardial infarction or pulmonary embolism, since anticoagulants may well be used for these; (3) the increasing incidence, apparently corresponding with the increase in age of population.

Nine cases are presented, with autopsy records, occurring between Jan. 1947-1951. In no case was there a correct antemortem diagnosis (except for a roentgenologist's diagnosis in one case which reached the ward after the patient's death). The cases are grouped according to presenting symptom complexes, i.e. (1) Cardiac—sudden severe chest pain. (2) Pulmonary—dyspnea, pain, signs of fluid in chest. (3) Neurologic-coma and hemiplegia; motor and sensory loss in peripheral nerve distribution. (4) Abdominal —nausea, vomiting, diarrhea, severe abdominal pain. (5) "Silent" dissecting aneurysm—in this case death due to subarachnoid hemorrhage, apparently unrelated to the aneurysm found at postmortem.

Chief clinical features and their incidence and relative importance in arriving at a diagnosis were listed as: (1) Age—majority 40-80 years. (2) Sex—men involved more frequently. (3) Race—nil noted. (4) B.P.—hypertension in 50-100%; persistence may be helpful in differentiating from infarction, where shock may occur. (5) Basal heart murmurs—diastolic are emphasized by some; not noted here. (6) Syphilis—not thought to be significant. (7) Arteriosclerosis—not present in 8 of the cases reviewed. (9) History of physical strain—may be significant; may be no co-existing medial aortic disease. (9) Congenital defect—previous reports emphasized coarctation or stenosis of aorta; Marfan's syndrome. (10) Pregnancy—has been reported. (11) Survival —60% die in 24 hours.

Laboratory findings, of white and red cell counts, urinalysis and chest X-ray, and E.C.G. are reported.

The pathology is reviewed as are theories of pathogenesis. Some emphasis

is placed on the idea of medial degeneration plus rupture of vasa vasora. Intimal rupture may occur secondarily. There was no correlation between extent of dissection and survival time.

The chief cause of death is hemopericardium—70%; hemothorax accounts for 20%.

S. Baker

Findings from Lingual Scrapings Taken During Treatment with Chloramphenical and Aureomycin: Tomaszewski W., Jour. of Clin. Path, **4**: 4, Nov. 1951.

This is a report on the examination of scrapings from the tongue of 126 patients receiving treatment with chloramphemical and aureomycin.

These antibiotics in the majority of these patients caused the disappearance of the normal bacterial flora and in the rest a marked diminution in the number of the bacteria. Sometimes new strains of bacteria appeared, presumably strains resistant to these antibiotics.

Epithelial cells are abundant in the first days of treatment and later increased numbers of characteristic blotchy epithelial cells often appear.

In the majority of patients fungus flora (usually *Candida albicans*) replace the bacterial flora. There was an associated increase in the number of leucocytes, suggesting that there is an inflammatory reaction to the fungal infection when bacteria are absent.

Clinically the tongue most often loses its whitish coat and shows a slight atrophy of the papillae, but in extreme cases there is marked atrophic glossitis with soreness and redness of the tongue. Some cases, however, show a hypertrophy of the mucosa with overgrowth of the papillae and brown discoloration. Fungi are scanty in the atrophic glossitis but profuse in the hypertrophic type.

There is a remarkable resemblance between oral changes from antibiotic therapy and those from vitamin B deficiency. This may be an actual vitamin B deficiency produced by destruction of intestinal flora, or the antibiotics may block intracellular metabolism to produce a change resembling vitamin B deficiency.

The results indicate that normal bacterial flora are necessary for the healthy structure and function of mucous membranes. Perhaps these bacteria have a protective action in defending mucous membranes against invasion by fungi.

J. B. Redford

Non-operative Treatment of Perforated Duodenal Ulcer: Seely S. F., Postgrad. Medicine, **10**: 5, Nov., 1951.

Since the introduction of the antibiotics there has been much interest in non-operative treatment of perforated peptic ulcer. The body mobilizes its defences against this condition amazingly rapidly and very frequently at operation the perforation is found to be healed. In an attempt to reduce the number and severity of surgical complications this study of medical management of perforated duodenal ulcer in 106 cases was undertaken.

Sixteen complications occurred and there was only one death—a death due to myocardial infarction. This compares very favorably with surgical treatment where complications occurred in 25% and death in 10% on the average of several series of cases. 103 of the patients treated were males mostly between 20 and 40 years of age. In 82 cases air was present under the diaphragm and in 90 cases treatment was instituted less than 12 hours after perforation—the period generally considered best for surgical intervention.

The treatment consisted of:

1. Constant decompression of the stomach with a Levin tube—the most important single feature of treatment.
2. Intravenous fluid administration.
3. Penicillin, streptomycin and sulfadiazine mostly given by intravenous drip.
4. Adequate sedation.

After about 6 days the tube was removed and diet gradually increased. Patients were followed for several weeks to rule out complications, but no follow-

up was done with reference to freedom from peptic ulcer symptoms.

It is stressed that for maximum success with this conservative management there must be constant attention to treatment and to the threat of complications. This may well be a better treatment than surgery in cases which are improving 24 hours after perforation, which have no air under the diaphragm, and in which the diagnosis is doubtful. However, until more cases are reported the internist should work in close collaboration with the surgeon before employing conservative means.

J. B. Redford

Diseases and Disorders of Muscle Function: D. McEachern. Bull. New York Acad. Med., 27: 3-23 1951.

This paper discusses the myotonias, myasthenia gravis, thyroidal neuromuscular disorders, progressive muscular dystrophy, the periodic paralyses, and menopausal muscular dystrophy.

Myotonia is a peripheral mechanism consisting of prolonged contraction of a muscle or part of a muscle after cessation of stimulation. The myotonic muscle is abnormally sensitive to the potassium ion. It is improved by quinine. Cortisone abolishes the condition but it returns when the hormone is discontinued.

Myasthenia gravis is characterized by weakness and undue fatiguability of skeletal muscle. It resembles curare poisoning, and results from deranged neuromuscular transmission. Some have attributed a curare-like action to the thymus and somewhat encouraging results have been achieved by thymectomy. Both ACTH and cortisone appear to make the myasthenia patient worse.

Thyroidal neuromuscular disorders. Weakness and fatiguability are prominent in uncomplicated hyperthyroidism. Disorders include exophthalmic ophthalmoplegia, acute thyrotoxic encephalomyopathy, chronic thyrotoxic myopathy, periodic paralysis, and myasthenia gravis.

Progressive muscular dystrophy. The muscle slowly degenerates and is ultimately replaced by fat and fibrous tissue. Secondary vascular changes occur. Creatinuria is a characteristic finding. Males are more commonly afflicted and there is a familial tendency. Treatment with wheat germ oil and alpha-tocopherol has been disappointing.

Periodic familial paralysis is characterized by flaccid paralysis mainly of the trunk and limb muscles. Attacks are frequently associated with thyroid struma and tend to occur after thyroid administration, epinephrine or diets high in carbohydrate. Many workers attribute the condition to faulty potassium metabolism.

Menopausal muscular dystrophy occurs in the late forties or thereafter and is characterized by a weakness of the girdle muscles. Three out of five respond to wheat germ therapy. Most patients respond dramatically to cortisone but relapse when the drug is withheld.

Juanita Casselman

NEWS AND NOTES

Medical Society

The Medical At Home will be held this year on Wednesday evening, February the 20th, at the Royal York Hotel. The Great Hall, which will be decorated in keeping with the theme, "The Doctor's Dilemma", will have Benny Lewis and his orchestra; the Crystal Ballroom, similarly decorated, will have music provided by a novel group.

Fraser Mustard, chairman of the group organizing the dance, said that the theme, "The Doctor's Dilemma", has allowed an interesting approach to the decorations as well as a new method of presenting this year's entertainment. The dress will be optional and corsages, in a variety of colours will be available at the door. The energies and imagination of the undergraduate body throughout all the years have been utilized in planning the dance. Directing the organization of this event were Fraser Mustard, chairman, and the year presidents, Geoff Secord 5T2, Fred Fallis 5T3, Ezra Silverstein 5T4, Tom McCulloch 5T5, Bill McIlroy 5T6 and Sandy Lowden 5T7.

* * *

Fred Fallis, 3rd meds, reports that a total of approximately one-hundred and twenty dollars was collected from Medical students after the showing of the film, "Story of a Red Feather". This amount greatly exceeds the contribution of the Medical students to the Red Feather Campaign in previous years.

* * *

Active in organizing the campaign SHARE is vice-president of the Medical Society, Fraser Mustard. The campaign to raise funds for the relief of Asian students took place during the week of Jan. 14-18.

* * *

At a recent Medical Society meeting, it was suggested that Medical students might be interested in having a school tie in Meds colours—wine and black. Peter Hopkins, 1st Medical year, is investigating the cost of this bold venture.

* * *

The Charles E. Frosst scholarship was given to Mr. P. S. Rosen, 4th Medical year, for his winning article which can be found on page 143 of this journal. Mr. Rosen is also president of the Medical Athletic Association.

* * *

E. M. Culp of 2nd Meds was awarded the Baptie Scholarship, A. N. Lofchi, also of 2nd Medical year, won the B'nai B'rith Scholarship. Other bursaries which were awarded recently was the RCAMC Women's Auxiliary Bursary to R. C. Rhodes and the Scottish Rite Masons' Bursary to J. C. Stears, 2nd Meds.

* * *

Faculty

Dr. William Edward Gallie, Professor Emeritus of Surgery at the University of Toronto, delivered the John Stewart Memorial Lecture on November 7th, 1951, at Dalhousie University, Halifax. Dr. Gallie, who spoke on "Teaching and Research in Surgery", is the first Canadian to have presented this memorial lecture.

* * *

Dr .Charles H. Hanes has recently arrived from Cambridge to take up his post as Professor of Biochemistry.

* * *

The Medical Alumni Association has announced the winners of the Medical Alumni Association Scholarships. They are Mr. P. Freeman, 4th medical; Mr. G. Y. Hirachi, 3rd medical; Mr. G. C. Stears, 2nd medical; Mr. M. E. Miller, 1st medical; Mr. H. J. Hoffmann, 2nd pre-medical, and Mr. K. O. McCuaig of the 1st pre-medical year.

The President of the Homewood Sanitarium of Guelph, Ontario, announces the retirement of Dr. F. R. C. Baugh, graduate of Queen's University, 1922, from his position as Medical Superintendent because of ill health. Dr. A. L. MacKinnon, a graduate of the University of Toronto, 1924, and formerly Assistant Medical Superintendent, has been appointed to suceed Dr. Baugh, and Dr. G. S. Burton, a graduate of Queen's University, 1931, of the Homewood Sanitarium staff has been appointed Assistant Medical Superintendent.

* * *

Two distinguished Medical scientists visited this University early in January, and delivered addresses to the Physiological Society on successive days. Professor K. J. Franklin of St. Bartholomew's Hospital Medical College, London, England, discussed the Fetal Circulation and Cardiovascular System and the changes they undergo at birth, illustrating his talk with some fascinating moving pictures. The following day, Dr. Harry Goldblatt, Director of the Institute for Medical Research at the Cedars of Lebanon Hospital at Los Angeles, spoke on the Humoral Mechanism of Hypertension, describing at some length his experiments with *renin* and *hypertensinogen*. Both addresses were enthusiastically received.

* * *

Dr. J. E. Howard of Johns Hopkins Hospital visited the Department of Medicine recently.

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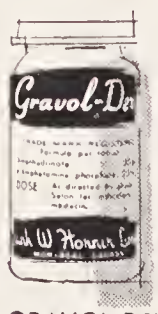

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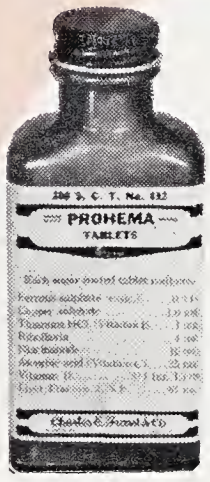

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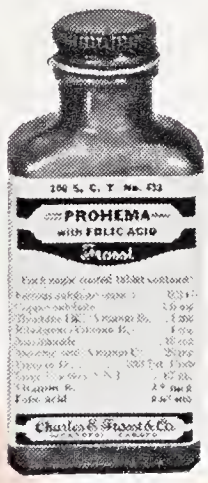

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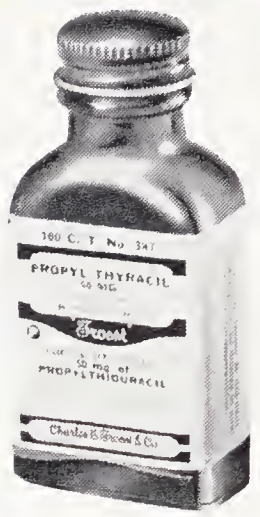

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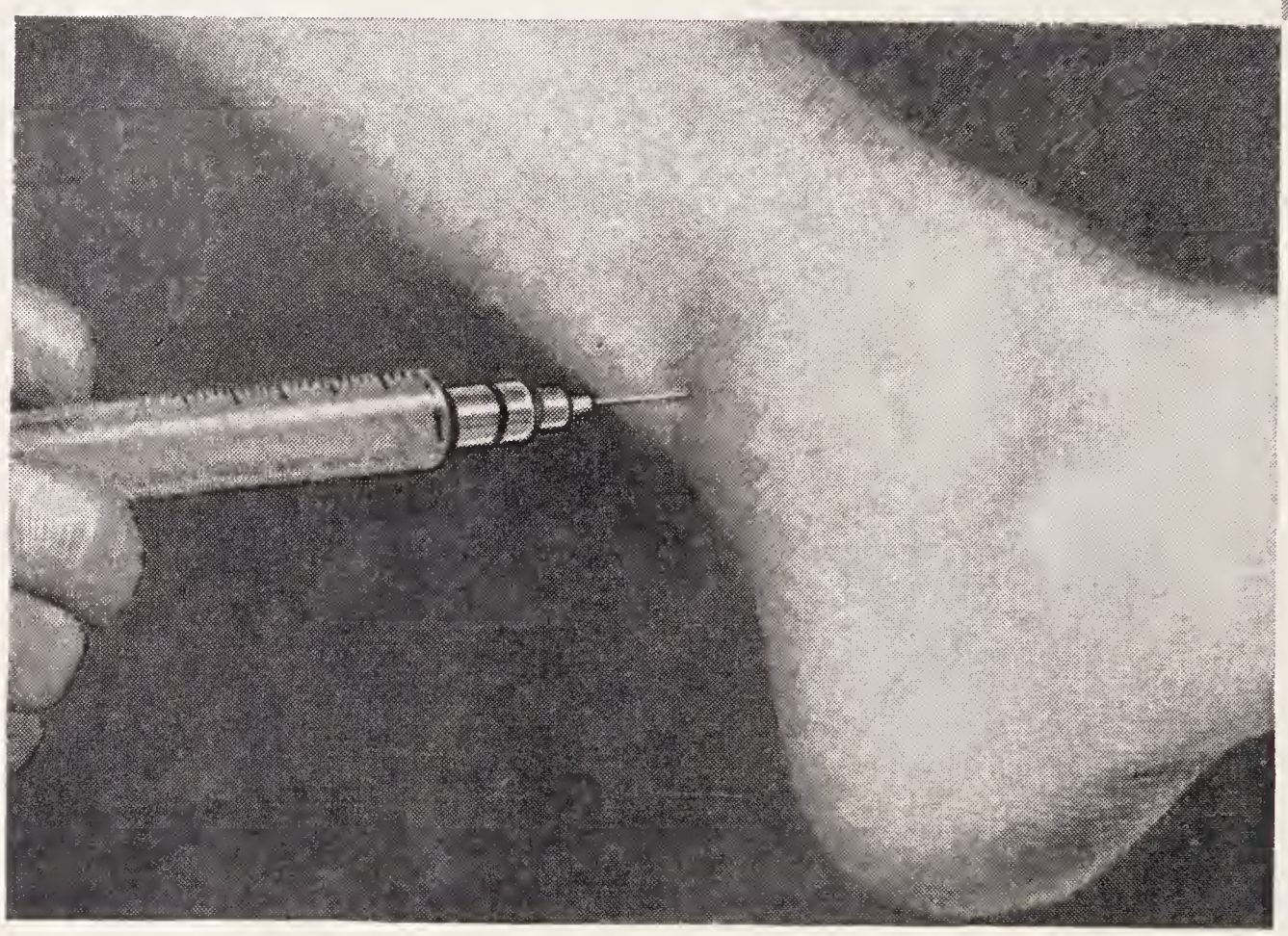

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